DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

SENT VIA ELECTRONIC MAIL

Chad A. Landmon
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90 Statehouse Square
Hartford, CT 06103-3702

Docket No. FDA-2009-N-0184

Dear Mr. Landmon:

By letters dated January 28, 2009, and February 6, 2009, to Gary Buehler, Director of the Office of Generic Drugs at the Food and Drug Administration (FDA or the Agency) on behalf of Actavis Elizabeth, LLC (Actavis), you have requested that the Agency reconsider its grant of "new chemical entity" exclusivity under section 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108 to Vyvanse (lisdexamfetamine dimesylate). New Drug Application (NDA) 21-977 for Vyvanse is held by Shire Development, Inc.

The Agency has determined that the issues raised in your correspondence are likely to be of interest to the public, that members of the public may wish to comment on the legal and regulatory issues raised in your submissions, and that the Agency's resolution of these issues could benefit from consideration of these comments. Therefore, as previously discussed with you, we are opening a public docket to solicit comment on certain legal and regulatory issues raised in the document you submitted on February 6, 2009, which is entitled "NCE Exclusivity for Lisdexamfetamine Dimesylate Capsules." Your February 6, 2009 correspondence and this letter opening the docket are being posted on the website for FDA's public dockets at http://www.regulations.gov.

So that we have the opportunity to fully consider comments from all interested parties, we are asking that all interested parties submit their comments to http://www.regulations.gov by close of business on June 1, 2009. Please include docket number FDA-2009-N-0184 in your correspondence. If you have any questions regarding this correspondence, please contact Susan Levine at 240-276-9313.

Sincerely,

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

cc: Shire Development, Inc.

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February 6, 2009

VIA HAND DELIVERY

Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation Research
Food and Drug Administration
7500 Standish Place, HFD-600
Rockville, MD 20855

Re: NCE Exclusivity for Lisdexamfetamine Dimesylate Capsules

Dear Mr. Buehler:

Following up on our January 27, 2009 letter, enclosed please find our legal brief in support of Actavis Elizabeth LLC's position that FDA should rescind the new chemical entity exclusivity granted to Shire Development, Inc. for its lisdexamfetamine dimesylate product (Vyvanse®). Actavis has submitted an ANDA for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg, referencing Shire's NDA No. 21-977. Actavis' ANDA has been pre-assigned ANDA No. 91-213. In our original ANDA submission, we requested that FDA rescind the NCE exclusivity granted to Vyvanse® and accept Actavis' ANDA for filing.

Based on our conversation with Elizabeth Dickinson in the Office of the Chief Counsel, we agreed to submit a legal brief with the ANDA to assist the agency in resolving the exclusivity issue during the agency's review of the ANDA for filing. For the time being, we request that this brief be kept confidential.

CONFIDENTIAL

We reserve the right to submit supplemental information to FDA in support of this request. We respectfully request a meeting with your office and with the Office of the Chief Counsel to discuss these issues at your earliest convenience.

Sincerely,

Chad A. Landmon

cc: Jeffrey M. Senger, Esq. (via hand delivery)
Elizabeth H. Dickinson, Esq. (via hand delivery)

ERRONEOUS AWARD OF NCE EXCLUSIVITY TO VYVANSE®

We represent an ANDA filer with respect to a recently submitted abbreviated new drug application ("ANDA") for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg, referencing new drug application ("NDA") No. 21-977 owned by Shire Development Inc. ("Shire"). We write to request that FDA rescind the new chemical entity ("NCE") exclusivity granted to Shire for its lisdexamfetamine dimesylate product (Vyvanse®) and accept the ANDA for filing.

Vyvanse is not entitled to NCE exclusivity because its active ingredient, dextroamphetamine, was previously approved. Specifically, FDA's grant of NCE exclusivity for Vyvanse should be rescinded because:

(1) Under a proper construction of 21 U.S.C. § 355(j)(5)(F)(ii), "active ingredient" should mean active moiety, which is the molecule or ion (or portion thereof) responsible for the therapeutic effect at the site of drug action;

(2) Lisdexamfetamine dimesylate is merely a carrier used by Shire to deliver the active moiety, dextroamphetamine, to the site of drug action. Lisdexamfetamine is not pharmacologically active and does not bind at the site of drug action; and

(3) Dextroamphetamine was approved in other applications well before the Vyvanse NDA was approved.

In granting NCE exclusivity to Vyvanse, FDA appears to have applied a blanket rule that all covalent derivatives other than esters should be considered "active ingredients" (or "active moieties"), while non-covalent derivatives should not. This rigid distinction between covalent and non-covalent derivatives, however, is arbitrary and capricious and contrary to the plain meaning of the statute and its legislative history. Specifically, Section 505(j)(5)(F)(ii) directs that NCE exclusivity be based on the approval of a new "active ingredient," which in the context of this provision means a new active moiety. The active moiety, in turn, is the molecule or ion (or portion thereof) that provides the therapeutic effect at the site of drug action. FDA's blanket distinction between covalent derivatives and non-covalent derivatives for purposes of awarding NCE exclusivity is inconsistent with the statute, its legislative history and, indeed, FDA's own regulations. Instead, an award of NCE exclusivity should focus on the active moiety, i.e., the molecule or ion (or portion thereof) that provides the therapeutic effect at the site of drug action.

Here, there can be no dispute that dextroamphetamine is the active moiety in Vyvanse that provides the therapeutic effect at the site of drug action. In fact, as discussed more fully below, Shire has represented to FDA and the public on numerous occasions that lisdexamfetamine has no activity and is absorbed in the gastrointestinal tract and cleaved, leaving the dextroamphetamine to travel to and act on the site of drug action in the brain.[1] Because dextroamphetamine was approved in numerous NDAs prior to the approval of Vyvanse, the

[1] To be clear, we are not suggesting that all newly-approved covalent derivatives are not entitled to NCE exclusivity. Instead, our request is limited to lisdexamfetamine, due to its mechanism of action.

award of NCE exclusivity to Vyvanse was improper, and the ANDA should be accepted for filing.[2]

BACKGROUND

Shire is the holder of NDA No. 21-977, pursuant to which it obtained approval to market lisdexamfetamine dimesylate capsules under the brand name Vyvanse. Shire markets Vyvanse for the treatment of attention deficit hyperactivity disorder ("ADHD"). FDA granted Vyvanse NCE exclusivity, which is set to expire on February 23, 2012.

The active ingredient in Vyvanse is listed in the Orange Book as lisdexamfetamine dimesylate. Lisdexamfetamine dimesylate is an amide conjugate (a covalent derivative) of dextroamphetamine. Lisdexamfetamine is formed by covalently attaching lysine to dextroamphetamine.

A covalent bond is a bond formed between two or more atoms by a sharing of electrons. (See Exhibit A, Theodore L. Brown, H. Eugene LeMay, Jr. & Bruce E. Bursten, Chemistry: The Central Science 255 (Tim Bozik ed., Prentice-Hall) (1997)). Examples of common covalently-bonded molecules include amide conjugates and esters. A non-covalent bond, on the other hand, is a bond that does not involve the sharing of pairs of electrons. Ionic bonds and hydrogen bonds are two examples of non-covalent bonds. An example of a typical non-covalently-bonded molecule is a salt.

According to the product insert, "Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity." (Exhibit B, Vyvanse Product Insert.) The product insert goes on to state:

> Lisdexamfetamine is converted to dextroamphetamine and L-lysine, which is believed to occur by first-pass intestinal and/or hepatic metabolism. Lisdexamfetamine is not metabolized by cytochrome P450 enzymes . . . Plasma concentrations of unconverted lisdexamfetamine dimesylate are low and transient, generally becoming non-quantifiable by 8 hours after administration.

(Id.) FDA reviewers confirmed this assessment:

> In its intact form lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the gastrointestinal tract, releasing active d-amphetamine. Lisdexamfetamine is an amide conjugate comprised of L-lysine covalently bound to the amino group of d-amphetamine.

(Exhibit C, Clinical Review, Dec. 6, 2005 at 7.) The Division of Psychiatric Products agreed:

> All the available evidence indicates that [lisdexamfetamine] is inactive, including both in vitro assays and in vivo animal data. In vitro assays showed that lisdexamfetamine has

[2] Shire will still be entitled to three years of exclusivity for Vyvanse under 21 U.S.C. § 355(j)(5)(F)(iii) in light of the studies Shire performed in support of its NDA.

> no activity at DA, NE, and a variety of other receptors. In vivo assays suggest that all the activity of orally administered lisdexamfetamine is due to the d-amphetamine that is released from the prodrug.

(Exhibit D, Thomas P. Laughren, Director, Division of Psychiatric Products, February 21, 2007 Memo at 2.)

In addition to statements Shire made to FDA and FDA's own findings, statements in U.S. Patent No. 7,223,735 ("the '735 patent," Exhibit E), which is owned by Shire and listed in the Orange Book for Vyvanse, are consistent with these findings. The '735 patent specification describes lisdexamfetamine as providing "a carrier and amphetamine which are bound to each other but otherwise unmodified in structure." (Exhibit E, '735 patent, col. 4, ll. 48-50.) The '735 patent goes on to state that lisdexamfetamine "does not cross the blood brain barrier and is thus substantially absent from the central nervous system," (id. at col. 9, ll. 15-17), and that "the covalent modification may prevent stimulant activity by preventing the drug from crossing the blood-brain barrier." (Id. at col. 10, l. 66 – col. 11, l. 1.) Finally, the claims of the '735 patent also describe the lisdexamfetamine as releasing "amphetamine as an active." (See, e.g., id., claims 1 and 18.)

Therefore, it is the dextroamphetamine in Vyvanse that provides the therapeutic effect at the site of drug action after the lysine is cleaved from the lisdexamfetamine before crossing the blood-brain barrier. Lisdexamfetamine is simply a carrier for the active moiety dextroamphetamine when it is administered; lisdexamfetamine itself is not pharmacologically active and does not provide any therapeutic effect.

Vyvanse is not the first drug approved by FDA where dextroamphetamine is the active moiety providing the desired therapeutic effect. In 1976, FDA approved an NDA for Dexedrine. The active ingredient in Dexedrine is dextroamphetamine sulfate, which is a salt (a non-covalent derivative) of dextroamphetamine. Dexedrine is indicated for the treatment of ADHD, as well as for narcolepsy. (Exhibit F, Dexedrine Prescribing Information.) In fact, FDA has approved numerous products in which dextroamphetamine is an active ingredient, including, for example, Adderall and Biphetamine.

The identical chemical entity (dextroamphetamine) is responsible for the pharmacological activity of Vyvanse, Dexedrine and these other dextroamphetamine-containing products. The only difference lies in its chemical form before ingestion. For example, the sulfate group in Dexedrine is attached to dextroamphetamine by a non-covalent bond to form a salt, as is the dimesylate group to the lisdexamfetamine in Vyvanse. The l-lysine amide conjugate in Vyvanse, however, is attached to dextroamphetamine by a covalent bond to form lisdexamfetamine.

DISCUSSION

Section 505(j)(5)(F)(ii) directs that NCE exclusivity be based on the approval of a new "active ingredient," which in the context of this provision means a new active moiety. The active moiety is the molecule or ion (or portion thereof) that provides the therapeutic effect at the

site of drug action. NCE exclusivity should only be granted if this active moiety was not previously approved by FDA.

FDA's application of a blanket rule that all covalent derivatives other than esters are "active ingredients" (or active moieties) under section 505(j)(5)(F)(ii) while all non-covalent derivatives are not is arbitrary and capricious and inconsistent with the statute and its legislative history, as well as other FDA regulations. Instead, the statute and regulations require that exclusivity be based on the active moiety, i.e., the specific molecule or ion (or portion thereof) that provides the therapeutic effect. Given that lisdexamfetamine has no pharmacological activity at the site of drug action, lisdexamfetamine cannot be considered an "active ingredient" under the NCE provision. Because dextroamphetamine, the active moiety in Vyvanse, was previously approved in earlier NDAs for Dexedrine and other products, Vyvanse is not entitled to NCE exclusivity and FDA should accept the ANDA for filing.

FDA's Blanket Distinction Between Covalent
And Non-Covalent Derivatives is Contrary to
The Statutory Language and its Legislative History

The Hatch-Waxman Amendments provide that FDA may grant NCE exclusivity to a drug "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application . . . ." 21 U.S.C. §355(j)(5)(F)(ii). FDA's absolute distinction between covalent and non-covalent derivatives as it has been applied in the NCE award to lisdexamfetamine is arbitrary and capricious and inconsistent with this statutory language and the legislative history.

Before its final regulations were issued, FDA originally interpreted the entire statutory phrase "active ingredient (including any ester or salt of the active ingredient)" to refer to an "active moiety." This statutory interpretation was subjected to court scrutiny in Abbott Labs. v. Young, 920 F.2d 984 (D.C. Cir. 1990). While this case was pending, FDA subsequently issued a letter ruling in which FDA construed only the initial reference to "active ingredient" (prior to the parenthetical) to refer to an "active moiety." (Exhibit G, July 26, 1989 letter from Ronald G. Chesemore, Acting Associate Commissioner for Regulatory Affairs to John D. Seigfried, M.D., Executive Director, Regulatory Affairs at McNeil Pharmaceutical ("the McNeil Letter").) Although the Court of Appeals did not expressly rule on this interpretation given that it was not the basis of the administrative decision at issue, the Court did suggest that this interpretation was proper. See Abbott Labs., 920 F.2d at 987 (discussing FDA's statutory interpretation in the McNeil Letter) and 992 (in which the dissent asserts that the majority gave a "strong hint" about how the agency should construe the statutory language). Significantly, the Court of Appeals characterized the "active moiety" as "the substance that creates the actual therapeutic effect within the body." Id. at 986.

Following the decision in Abbott, FDA issued its final regulations and confirmed its interpretation that "active ingredient" in Section 355(j)(5)(F) should be construed to mean "active moiety." (See Exhibit H, Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (Oct. 3, 1994).) In the final rule, however, FDA arbitrarily drew a rigid distinction between covalent and non-covalent derivatives. In particular, FDA defined "new chemical entity" to mean "a drug that contains no *active moiety*

that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 C.F.R. § 314.108(a) (emphasis added). "Active moiety," in turn, is defined as:

> the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Id. Finally, "drug substance" is defined as "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use (*sic*) in the synthesis of such ingredient." 21 C.F.R. § 314.3(b).

The practical result of these regulations is that a non-covalent derivative of a previously-approved active moiety will not be entitled to NCE exclusivity, but a covalent derivative of a previously-approved active moiety will be, regardless of the identity of the molecule or ion (or portion thereof) responsible for the therapeutic action of that derivative. FDA set forth its reasoning for this distinction in the McNeil Letter, including distinguishing esters (which are covalent derivatives):

> [a]lthough forming an ester causes a change in the covalent structure of the molecule, formation of an ester is more analogous to changes in noncovalent structures than to other changes in covalent structure. Portions of a molecule that are not covalently bound to the molecule, such as those portions that cause a drug to be a salt or complex, are designed to be separated from the "active moiety" before the drug is absorbed into the circulation. These noncovalently bound portions do not travel to, or act on, the site of drug action. Covalently bound portions, on the other hand, generally remain part of the active moiety and travel to the site of drug action. The formation of an ester, unlike other covalently bound groups, is in almost all cases designed to be removed before, or just after, absorption by gut or blood esterases; at that point the ester portion is cleaved from the "active moiety," and only the active moiety travels to, and acts on, the receptor site.

(Exhibit G, McNeil Letter at 12, fn. 5.) These generalities about covalent and non-covalent derivatives, however, do not reflect what happens when Vyvanse is administered and do not support the award of NCE exclusivity. Moreover, the arbitrary distinction between covalent and non-covalent derivatives is contrary to the plain language of the statute and its legislative history.

As an initial matter, Section 505(j)(5)(F)(ii) does not mention derivatives other than the esters and salts cited as examples in the parenthetical phrase quoted above. The statute does not suggest a distinction between covalent derivatives (such as esters) and non-covalent derivatives (such as salts), nor a Congressional intent to award exclusivity to covalent derivatives but not to non-covalent derivatives. On the contrary, the plain language establishes that Congress made no distinction between covalent and non-covalent derivatives, as the two examples mentioned in the parenthetical include both covalent derivatives and non-covalent derivatives. There is simply no support in the statutory language for a blanket distinction between covalent derivatives and non-covalent derivatives.

The legislative history further undermines such a distinction. According to Representative Waxman, NCE exclusivity was designed to "give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains." (Exhibit I, 130 Cong. Rec. H9113 (daily ed. Sept. 6, 1984).) He later elaborated that "Congress wanted to assure that drug companies were rewarded for major *innovations* involving . . . a new drug . . . by guaranteeing them a period of market exclusivity during which time they could recoup their developmental costs." (Exhibit J, Letter from Congressman Henry A. Waxman to Frank E. Young, Commissioner, Food and Drug Administration, August 5, 1985 at 1.) In the McNeil Letter, FDA confirmed "that in using the phrase 'active ingredient (including any ester or salt of the active ingredient)' . . . , Congress intended to refer to new active moieties and to confer 5 years of exclusivity only on never-before-approved active moieties." (Exhibit G, McNeil Letter at 4.)

Thus, there is no support in the statute or its legislative history for an interpretation that deems covalent derivatives of previously-approved drugs (other than esters) "major innovations" entitled to NCE exclusivity, while non-covalent derivatives of the same drugs are not. Nowhere did Congress draw a blanket distinction between covalent and non-covalent derivatives; FDA must follow this clear Congressional intent.

When it proposed Section 314.108 and defined active moiety, FDA explained that it was excluding non-covalent derivatives from classification as new chemical entities, but that a "compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety is considered a 'new molecular entity' . . . and will be considered a new chemical entity entitled to 5 years of exclusivity." (Exhibit K, Preamble to proposed Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,897 (July 10, 1989).) FDA did so, however, without explaining how the distinction between covalent and non-covalent derivatives could be squared with the statutory language. Moreover, FDA left the door open for further consideration of an award of exclusivity to a particular covalent derivative, stating that "FDA will consider whether a drug contains a previously approved active moiety on a case-by-case basis." (Id.)

The arbitrary nature of FDA's distinction between covalent and non-covalent derivatives comes into sharp focus with lisdexamfetamine. As discussed in further detail below, lisdexamfetamine has no pharmacological activity. Instead, it is cleaved after ingestion, and dextroamphetamine is the only molecule that travels to and acts on the site of drug action. Indeed, while lisdexamfetamine is chemically a covalent derivative, it essentially behaves like esters and salts, which Congress expressly determined were not new "active ingredients." In fact, lisdexamfetamine behaves essentially the same as non-covalent derivatives. Because lisdexamfetamine acts like an ester, salt or other non-covalent derivative, there is no basis to treat it differently than these compounds based on an arbitrary distinction between covalent and non-covalent derivatives.

Given the fact that there is no basis in the statute for distinguishing between covalent and non-covalent derivatives, FDA must deny NCE exclusivity to Vyvanse or, at a minimum, evaluate whether Vyvanse does anything more than deliver the active moiety dextroamphetamine to the site of drug action.

Dextroamphetamine is the "Active Ingredient" in Vyvanse Because it is the Therapeutically Effective Moiety

Rather than distinguishing between covalent and non-covalent derivatives, the reference in the statutory NCE exclusivity provision to "active ingredient" and the agency's regulations establish that exclusivity must be based on the approval of a new active moiety, i.e., the molecule or ion (or portion thereof) that provides the therapeutic effect at the site of drug action. Here, there can be no dispute that it is the dextroamphetamine in Vyvanse that provides the therapeutic effect at the site of action. Given that dextroamphetamine had been approved in numerous NDAs prior to the approval of Vyvanse, FDA's grant of NCE exclusivity was improper.

As previously discussed, the NCE exclusivity provision refers to an "*active* ingredient." 21 U.S.C. § 355(j)(5)(F)(ii) (emphasis added). Congress intentionally used the word "active" to modify "ingredient." The word "active" must be given meaning, and it clearly refers to the ability to render the therapeutic effect on the body.

In fact, FDA recognized the active/inactive distinction when it defined "new chemical entity" to mean "a drug that contains no *active* moiety that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 C.F.R. § 314.108(a) (emphasis added). FDA then defined "active moiety" to mean "the molecule or ion . . . *responsible for the physiological or pharmacological action* of the drug substance." Id. (emphasis added). It recognized the same active/inactive distinction in defining "drug substance" to mean "an active ingredient that is *intended to furnish pharmacological activity* . . . ." 21 C.F.R. § 314.3(b).

Moreover, FDA's Good Manufacturing Practices ("GMP") regulations reflect the same active/inactive distinction and further demonstrate the manner in which the agency has distinguished between active and inactive components. Specifically, the GMP regulations define "active ingredient" to mean "any component that is *intended to furnish pharmacological activity* or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals." 21 C.F.R. § 210.3(7). "Inactive ingredients," on the other hand, encompass "any component other than an active ingredient." 21 C.F.R. § 210.3(8). The distinction is based on whether the component or ingredient is intended to cause the therapeutic effect; any other component is denominated an "inactive ingredient." While an inactive ingredient can cause a known physiological effect (such as a side effect or controlled release and absorption of a drug), that physiological effect does not result in the "inactive" ingredient being characterized as "active."

Thus, both the statute and FDA's regulations distinguish active versus inactive components based on whether the component provides the therapeutic effect. In the case of Vyvanse, there can be no dispute that dextroamphetamine is the molecule (or portion of the molecule) responsible for the therapeutic effect, and that dextroamphetamine was approved in many drug products prior to the approval of Vyvanse.

Specifically in Vyvanse, the molecule that is absorbed into the systemic circulation and goes to the site of drug action – dextroamphetamine – remains the same despite having been formulated into a covalent derivative for administration. All evidence indicates that the amide conjugate is cleaved from lisdexamfetamine, and only the active dextroamphetamine travels to

and works on the site of drug action at the DA and NE reuptake sites in the brain. As was repeatedly stated during FDA's review of the Vyvanse NDA, the data shows "that lisdexamfetamine does not bind at the DA and NE reuptake sites that underlie the sympathomimetic effects of amphetamines. Thus, on this basis, lisdexamfetamine would not be expected to have any amphetamine-like activity." (Exhibit L, Thomas P. Laughren, Director, Division of Psychiatry Products, Feb. 23, 2007 Memo at 1.) FDA reviewers further determined that "[i]n its intact form lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive." (Exhibit C, Clinical Review, Dec. 6, 2005 at 7.) In fact, "[i]n vivo assays suggest that *all the activity* of orally administered lisdexamfetamine is due to the d-amphetamine that is released from the prodrug." (Exhibit D, Feb. 21, 2007 Laughren Memo at 2.)

Moreover, Shire repeatedly represented to FDA and the public that dextroamphetamine is the only molecule responsible for the pharmacological activity in Vyvanse. According to the product insert, "[a]fter oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity." (Exhibit B, Vyvanse Product Insert.) When discussing the pharmacology of Vyvanse, the product insert only refers to dextroamphetamine, and there are no statements regarding the pharmacological activity of lisdexamfetamine. (Id.) The lack of statements relating to the existence of any clinically relevant difference in the safety or efficacy profile of lisdexamfetamine as compared dextroamphetamine in the product insert further indicates that the activity of Vyvanse is solely provided by dextroamphetamine.

In the Orange Book-listed '735 patent, lisdexamfetamine is described as providing "a carrier and amphetamine which are bound to each other but otherwise unmodified in structure." (Exhibit E, '735 patent, col. 4, ll. 48-50.) The '735 patent goes on to state that lisdexamfetamine "does not cross the blood brain barrier and is thus substantially absent from the central nervous system," (id., col. 9, ll. 15-17), and that "the covalent modification may prevent stimulant activity by preventing the drug from crossing the blood-brain barrier." (Id., col. 10, l. 66 – col. 11, l. 1.) Both Shire and New River Pharmaceuticals have also publicly stated in press releases that dextroamphetamine is responsible for Vyvanse's activity. (See, e.g., Exhibit M, Feb. 23, 2007 New River Press Release ("The combination [of dextroamphetamine covalently-linked to l-lysine] is rapidly absorbed from the gastrointestinal tract and converted to d-amphetamine, which is responsible for VYVANSE's activity."); Exhibit N, Oct. 25, 2007 Shire Press Release ("VYVANSE is a therapeutically inactive prodrug, in which d-amphetamine is covalently bonded to l-lysine, and after oral ingestion it is converted to pharmacologically active d-amphetamine.").)

Under the weight of evidence presented by Shire to FDA and to the public, and under FDA's own findings, there can be no credible dispute that dextroamphetamine is the only moiety in Vyvanse that has a therapeutic effect at the site of drug action. Thus, under both the wording of the statute and FDA's regulations, the NCE exclusivity grant to Vyvanse was improper because numerous products containing dextroamphetamine were approved prior to Vyvanse receiving FDA approval.

FDA's Active Moiety Regulation
Does Not Require a Different Approach

FDA's regulation defining "active moiety" is, on its face, consistent with the plain meaning of the statute, as well as with the agency's longstanding distinction between active and inactive components. As discussed above, the regulation provides:

> Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

21 C.F.R. § 314.108(a).

Properly interpreted, the regulation provides that the active moiety is the "molecule" that is "responsible for the physiological or pharmacological action of the drug substance," less the salt, ester or non-covalent appendage to that molecule. Here, the molecule responsible for the pharmacological action of the drug substance is dextroamphetamine. Dextroamphetamine has no salt, ester or other non-covalent appendage, and is thus the "active moiety" for purposes of exclusivity.

Although FDA has in the past interpreted the regulation differently, the prior interpretation need not and should not be applied here. Under the agency's previously expressed interpretation, the agency apparently deemed the "molecule" that is "responsible for the physiological or pharmacological action of the drug substance" to be the drug substance itself. Under this reading, the "molecule" entitled to exclusivity is the not the molecule providing the therapeutic effect at the site of drug action (less certain appendages), but is rather the active component found in the product formulation (less certain appendages) prior to administration. This interpretation, however, renders meaningless the requirement that the "molecule" at the beginning of the "active moiety" definition be "responsible for the physiological or pharmacological action of the drug substance." Moreover, this interpretation is circular – it defines "active moiety" as "drug substance" and "drug substance" as "active ingredient."

While FDA has voiced and, in some instances, applied this interpretation, the agency is not bound by it.[3] The agency must interpret and apply the regulation in a manner that does not contravene the statute. As the United States Court of Appeals for the District of Columbia has held, "a regulation which operates to create a rule out of harmony with the statute, is a mere nullity." Social Security Admin., Baltimore, MD. v. Fed. Labor Relations Auth., 201 F.3d 465,

[3]Even a reversal of a longstanding position does not undermine deference where the agency provides a rational explanation for its change. See, e.g., Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs., 545 U.S. 967, 981 (2005); General American Transportation Corp. v. Interstate Commerce Commission, 872 F.2d 1048, 1054 (D.C. Cir. 1989); Chevron, U.S.A., Inc. v. Natural Resources Defense Council, 467 U.S. 837, 857-58 (1984); Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 41-44 (1983). As the courts have noted, "it does not matter that [an agency] 'switched horses in midstream' as long as it 'was astraddle a good horse when it reached the other side.'" Texaco v. Department of Energy, 795 F.2d 1021, 1024 (Temp. Emer. Ct. App. 1986) cert. dismissed, 478 U.S. 1030 (1986) (citing Gulf Power Co. v. EPA, PCA No. 77-0477 (N.D. Fla. May 2, 1978)).

471 (D.C. Cir. 2000) (citing Manhattan Gen. Equip. Co. v. Commissioner of Internal Revenue, 297 U.S. 129, 134 (1936). See also Caldera v. J.S. Alberici Constr. Co., 153 F.3d 1381, 1383 n.** (Fed. Cir. 1998) ("Statutes trump conflicting regulations"). Here, the only reasonable interpretation that is consistent with the wording of the statute (as well as with the agency's longstanding distinction between active and inactive drug components) is an interpretation that would deem the "active moiety" to be the molecule that actually provides the therapeutic effect at the site of drug action.

CONCLUSION

Accordingly, FDA should rescind the NCE exclusivity awarded to Vyvanse because (1) dextroamphetamine is the moiety that is responsible for its therapeutic effect at the site of drug action; (2) dextroamphetamine was previously approved in numerous NDAs, including the NDA for Dexedrine; and (3) the provisions of the Hatch-Waxman Amendments preclude a grant of NCE exclusivity to an active moiety that was approved in a previous application. As a result, FDA should accept the ANDA for filing and its review should not be delayed. We respectfully request that FDA advise us of its position as soon as possible so that we may seek judicial relief should the agency refuse to file the ANDA.

Contents

...exhibits metallic ...lorine gas consists ...es, which contain ...nt bonds. The ...sodium and ...sodium chloride, ...bonding.

8 Basic Concepts of Chemical Bonding

On the table in most diners you can expect to find two white, crystalline substances: table salt and granulated sugar. In spite of their similarities in appearance, salt and sugar are vastly different in chemical composition. Table salt is sodium chloride, NaCl, which consists of sodium ions, Na^+, and chloride ions, Cl^-. Granulated sugar does not contain ions at all; rather, it consists of molecules of sucrose, $C_{12}H_{22}O_{11}$, in which there are strong *covalent bonds* between the atoms of each molecule. As we discussed in Chapter 4, NaCl dissolves in water to yield ions in solution—NaCl is an electrolyte—whereas an aqueous solution of sucrose contains sucrose molecules—sucrose is a nonelectrolyte. ∞ (Section 4.2)

Why are some substances composed of ions and others composed of molecules? The keys to answering this question are found in the electronic structures of the atoms involved, which we discussed in Chapters 6 and 7, and in the nature of the chemical forces within the compounds. In this chapter and the next we will examine the relationships among electronic structure, chemical bonding forces, and the properties of substances. As we do this, we will find it useful to classify chemical forces into three broad groups: (1) ionic bonds, (2) covalent bonds, and (3) metallic bonds. Figure 8.1 shows examples of substances in which we find these types of bonds.

The term **ionic bond** refers to electrostatic forces that exist between ions of opposite charge. Ions may be formed from atoms by the transfer of one or more electrons from one atom to another. Ionic substances generally result from the interaction of metals on the far left side of the periodic table with nonmetals on the far right side (excluding the noble gases, group 8A).

A **covalent bond** results from the sharing of electrons between two atoms. The most familiar examples of covalent bonding are seen in the interactions of nonmetallic elements with one another.

Metallic bonds are found in solid metals such as copper, iron, and aluminum. In the metals, each metal atom is bonded to several neighboring atoms. The bonding electrons are relatively free to move throughout the three-dimensional structure. Metallic bonds give rise to such typical metallic properties as high electrical conductivity and luster.

Let's begin our discussion in this chapter by examining the preferred arrangements of electrons in atoms when they form chemical compounds.

8.1 Lewis Symbols and the Octet Rule

The electrons that are involved in chemical bonding are called **valence electrons**. The term *valance* (from the Latin *valere*, "to be strong") relates to the formation of chemical bonds. Valence electrons are the electrons that reside in the incompletely filled outer electron shell of an atom. ∞ (Section 6.8)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-977
Submission Code	N
Letter Date	December 6, 2005
Stamp Date	December 6, 2005
PDUFA Goal Date	October 6, 2006
Reviewer Name	Michelle M. Chuen, M.D.
Review Completion Date	July 28, 2006
Established Name	Lisdexamfetamine Dimesylate Capsules
Trade Name	None
Therapeutic Class	Amphetamine
Applicant	New River Pharmaceuticals, Inc.
Priority Designation	S
Formulation	30, 50, and 70mg Capsules
Dosing Regimen	30-70 mg/day
Indication	Attention Deficit Hyperactivity Disorder
Intended Population	Children with Attention Deficit Hyperactivity Disorder

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement be granted approvable status. There are a number of requests[1] to which the sponsor has not yet responded. These responses will be reviewed in an addendum. In addition, it is recommended that further information be requested (see section 9.2). Final approval is contingent on satisfactory responses to the concerns conveyed in previous requests for information and in the approvable letter, satisfactory Final Clinical Study Report for Study 302, satisfactory DSI, CSS, Statistical, CMC, Pharm/Tox, and Biopharm reviews, and mutual agreement on labeling (see section 9.4).

1.1.1 Risk Management Activity

There are no additional recommendations.

1.1.2 Required Phase 4 Commitments

There are no additional recommendations.

1.1.3 Other Phase 4 Requests

There are no additional recommendations.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

The efficacy of oral lisdexamfetamine dimesylate (also referred to as NRP104) in the treatment of patients with attention deficit hyperactivity disorder (ADHD) is based on Studies 201 and 301.

[1] These requests are summarized as follows: 1) literature search, 2) enumeration of pre-marketing adverse events not reported in the >2% Table for the Safety Populations of Studies 201 and 301, 3) enumeration of ITT population patients using concomitant medications during the double-blind period of Study 201 and during Study 301, 4) enumeration of patients that were identified as protocol violators because of prohibited medication use for Studies 201 and 301, 5) serious adverse event definition, 6) mean change from baseline analyses for height and weight with adjustments for age and sex by converting to z-scores for Study 301, 7) outlier analyses for height and weight with adjustments for age and sex by converting to z-scores for Study 301, and 8) description of height and weight measurement methodology

Study 201 consisted of a 3-week Adderall XR open-label titration period followed by a randomized, double-blind 3-treatment, 3-period (one week each) double-blind fixed dose crossover period utilizing NRP104 doses of 30, 50, and 70 mg/day, Adderall XR doses of 10, 20, and 30 mg/day, and placebo. Study 301 was a randomized, double-blind, placebo-controlled, fixed dose trial of about 4 weeks' duration utilizing doses of 30, 50, and 70 mg/day.

The safety of NRP104 is based on Study 301, in which safety was evaluated in 218 NRP104 patients and 72 placebo patients. Deaths, serious adverse events and dropouts due to adverse events were examined for an additional 186 patients in the remaining ten studies (studies 102, 101, 104, 106, 103, 201, 302, A01, A02, and A03).

1.2.2 Efficacy

The sponsor has provided evidence from one crossover study (Study 201) and one parallel-group study (Study 301) with three doses of (30, 50, and 70 mg/day) that supports the claim of short-term efficacy for the use of NRP104 in attention deficit hyperactivity disorder. The primary efficacy variables in Studies 201 and 301 were the SKAMP-DS and the ADHD-RS, respectively.

1.2.3 Safety

A total of 404 patients received NRP104 and had safety data in eleven trials. Since Study 302 is still ongoing, complete safety data for this study is pending at this time. This submission revealed safety findings consistent with the previously observed safety profile of amphetamines.

1.2.4 Dosing Regimen and Administration

Study 301 was a fixed dose study of NRP104 that examined doses of 30, 50, and 70 mg/day versus placebo in the treatment of attention deficit hyperactivity disorder. All three dose groups produced a significant difference over placebo.

Patients were randomized to 30, 50, and 70 mg treatment groups. For all dose groups, dosing for NRP104 began at 30 mg/day for the first week of treatment. For the 50 and 70 mg treatment groups, dosage was increased to 50 mg/day at week 2. For the 70 mg treatment group, dosage was increased to 70 mg/day at week 3.

Based on drug/placebo comparisons, there was evidence of a significant treatment effect for the low dose ($p<0.0001$), and results at the two higher doses were similar in both robustness ($p<0.0001$) and magnitude of effect size (placebo-adjusted difference of -15.58, -17.21, and -20.49 for 30 mg, 50 mg, and 70 mg, respectively). The mean change from baseline at endpoint was -21.8 (SE=1.60), -23.4 (SE=1.56), and -26.7 (SE=1.54) for the 30 mg, 50 mg, and 70 mg groups, respectively. The difference between the 30 mg and 70 dose groups could be as small as 0.2 on a 54-point scale, which is unlikely to be clinically significant. Therefore, there appears to be no substantial advantage of the higher doses (50 and 70 mg) over the lower dose (30 mg).

In Study 201, since patients were not randomized to fixed doses in this trial, no assessment of dose-response was possible.

1.2.5 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

1.2.6 Special Populations

Age did not appear to significantly affect treatment response as measured by SKAMP-DS average and ADHD-RS change from baseline for Studies 201 and 301, respectively. Ethnicity appeared to affect treatment response for Study 301, but not for Study 201. There was insufficient information to determine the effect of gender or baseline severity of illness on outcome. Please see Section 6.1.4 for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

NRP104 is a novel product being developed as a once-a-day treatment for attention deficit disorder (ADHD) in pediatric populations (ages 6-12). The active ingredient in NRP104 capsules is lisdexamfetamine as the dimesylate salt, a new chemical entity. In its intact form lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the gastrointestinal tract, releasing active d-amphetamine. Lisdexamfetamine is an amide conjugate comprised of L-lysine covalently bound to the amino group of d-amphetamine.

The sponsor is seeking approval for treatment of children (ages 6-12) with attention deficit hyperactivity disorder (ADHD) with a dosing regimen of 30 to 70 mg/day based on the results of 2 completed clinical studies (1 Phase 2, 3-period crossover and 1 short-term fixed-dose).

2.2 Currently Available Treatment for Indications

The five moieties approved in the U.S. for the treatment of attention deficit hyperactivity disorder are: dextroamphetamine, mixed salts of a single entity amphetamine product (amphetamine/dextroamphetamine), methylphenidate, dexmethylphenidate, and atomoxetine.

2.3 Availability of Proposed Active Ingredient in the United States

Lisdexamfetamine has not been approved for use in the United States.

2.4 Important Issues with Pharmacologically Related Products

NRP104 is most closely related pharmacologically to dextroamphetamine and mixed salts of a single entity amphetamine product (amphetamine/dextroamphetamine). These products have been associated with several safety issues. Among the major safety issues are sudden death with structural cardiac abnormalities or other serious heart problems, hypertension, tachycardia, psychotic symptoms, manic symptoms, aggressive behavior or hostility, long-term suppression of growth, seizures, and visual disturbance.

2.5 Presubmission Regulatory Activity

An end-of-Phase 2 meeting request to discuss the development of NRP104 in the treatment of ADHD was submitted May 6, 2004, and the meeting was held on July 29, 2004. At the meeting, clinical issues addressed included: 1) agreement with additional pharmacokinetic studies, 2) concurrence with the overall design of the two proposed pediatric pivotal Phase 3 studies[2], 3) concurrence with the statistical approach and definition of the efficacy population, and 4) agreement that the overall clinical development plan was adequate and supported registration of the product for the treatment of ADHD in 6-12 year olds.

At the pre-NDA meeting on July 6, 2005, among the clinical issues addressed were the Agency's requests for 1) a summary of vital signs, 2) inclusion of weight in the vital signs assessments, 3) further breakdown of ethnicity, and 4) calculated z-scores for all longer term studies.

This NDA was submitted to the Agency on December 6, 2005. The Filing Meeting was held on January 24, 2006 and it was concluded that this supplement was fileable. The User Fee due date is October 6, 2006.

A 4-Month Safety Update to the NDA was submitted on April 11, 2006.

2.6 Other Relevant Background Information

The undersigned reviewer was unable to locate any information on withdrawal of the product in other countries, or on submission of marketing authorization applications to foreign regulatory agencies.

[2] Note that, although in the meeting, the sponsor referred to two Phase 3 studies as proposed pivotal studies, the briefing package contained protocols for two short-term efficacy studies [one Phase 2 (Study 201) and one Phase 3 (Study 301)] and one long-term safety study (Study 302).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

According to a 7/20/06 email from Lyudmila Soldatova, Ph.D., Chemistry reviewer, the sponsor claimed categorical exclusion from Environmental Assessment for this NDA. At the time of completion of this review, neither her CMC review nor a draft of her review was available.

3.2 Animal Pharmacology/Toxicology

At the time of completion of this review, neither a Pharmacology/Toxicology review nor a draft of the review was available. According to a 7/25/06 email from Barry Rosloff, Ph.D., Pharmacology/Toxicology Team Leader, there were no significant pharmacology/toxicology concerns.

3.3 Statistical Review and Evaluation

Yeh-Fong Chen, Ph.D., is the statistical reviewer for this NDA. Her written review is pending completion at this time. Based on a draft of her review, she has indicated that both efficacy studies (201 and 301) demonstrated efficacy of all three doses of NRP104. Nevertheless, she indicated that [redacted] cannot be granted [redacted]

3.4 DSI Clinical Site Inspections

The Division of Scientific Investigations (DSI) selected 3 sites for inspection. Two of the sites were from studies 201 and 301 [site 04 (Dr. Frank Lopez), and site 03 (Dr. Ann Childress)], and one of the sites was from Study 301 [site 37 (Dr. [redacted]]. Inspections for all sites have been completed. However, at the time of completion of this review, a Clinical Inspection Summary has not yet been completed by Jose Tavarezpagan, DSI Consumer Safety Officer.

According to the VAI (Voluntary Action Indicated-no response requested) letter sent to Dr. Childress, records for 11 subjects enrolled in Study 201 and 4 subjects enrolled in Study 301 from site 03 were reviewed by DSI. It was determined that the site did not conduct the investigation in accordance with the investigational plan. Deviations from the protocol included lack of a 30-day follow-up phone call for 2 patients in Study 201, and lack of hematology test at screening for one patient in Study 301. Overall, data generated from protocols NRP104.201 and NRP104.301 at this site appeared acceptable for use in support of this NDA.

Data from the remaining 2 sites for use in support of this NDA supplement is still pending.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The safety of NRP104 in the treatment of pediatric patients with attention deficit hyperactivity disorder is based on Study 301. Deaths, serious adverse events and dropouts due to adverse events were examined for the remaining ten studies (studies 102, 101, 104, 106, 103, 201, 302, A01, A02, and A03).

The efficacy of NRP104 in the treatment of pediatric patients with attention deficit hyperactivity disorder is based on studies 201 and 301. Study 201 consisted of a 3-week Adderall XR open-label titration period followed by a 3-week, 3-period double-blind fixed dose crossover period. Study 301 was a 4-week fixed dose study.

4.2 Tables of Clinical Studies

A total of eleven clinical trials comprise this application. These trials are summarized in the table below.

TABLE 4.2.1: NRP104 STUDIES

Phase I Studies	
Single-Dose	
102	Open-label, 3-treatment, 3-period, 6-sequence, randomized, crossover study to assess the relative bioavailability of d-amphetamine of NRP104 70 mg in 18 healthy subjects aged 18 to 55 when administered orally under 3 dosing conditions: an intact capsule only, a solution containing the capsule contents, and an intact capsule with high fat meal
101	Open-label, randomized, two-period crossover study to compare the rate of absorption and oral bioavailability of two dose levels (25 and 75 mg) of NRP 104 test formulation to oral doses of Dexedrine 30 mg and Adderall XR 35 mg in 20 healthy subjects aged 18 to 55
106	Open-label study to assess the distribution, metabolism, and elimination of NRP-104 radiolabel with ^{14}C in 6 healthy subjects aged 18 to 55
103	Open-label, 3-treatment, 3-period, 6 sequence, randomized, crossover study to asses dose proportionality of d-amphetamine after oral administration of 30, 50, and 70 mg of NRP104 after an overnight fast in 18 children with ADHD aged 6 to 12
Multiple-Dose	
104	Open-label study to assess steady state pharmacokinetics of NRP104 70 mg following 7-day once-daily administration in fasting 12 healthy subjects aged 18 to 55

Completed Phase 2/3 Studies	
201	Multi-center, randomized, double-blind, 3-treatment, 3-period (one week each) crossover study following an 3-week, open-label Adderall XR titration period to assess, in a controlled environment, the efficacy and safety of NRP104 (30, 50, or 70 mg) and Adderall XR (10, 20, or 30 mg) compared to placebo in 52 children with ADHD aged 6 to 12
301	Multi-center, randomized, double-blind, placebo-controlled, parallel-group fixed-dose, 4 week study to assess the efficacy and safety of NRP104 (30, 50, or 70 mg) compared to placebo in 297 children with ADHD aged 6 to 12
Ongoing Phase 2/3 Study	
302	Multi-center, open-label, and single-arm study to assess the safety of NRP104 (30, 50, or 70 mg) for up to one year in children with ADHD aged 6 to 12. As of the NDA submission, 273 patients have been enrolled.
Abuse Studies	
A01	Single-center, single-blind, 2 month study to determine the safety and tolerability of increasing single oral doses of NRP104 (up to 150 mg) compared to placebo and d-amphetamine sulfate 40 mg and to gather preliminary estimates of abuse liability in 12 subjects with a history of stimulant abuse aged 18 to 55
A02	Single-center, double-blind, randomized study to determine the safety, tolerability, and abuse liability of single intravenous doses of NRP104 25 and 50 mg compared to placebo and d-amphetamine sulfate in 12 subjects with a history of stimulant abuse aged 18 to 55
A03	Single-center, double-blind, randomized, placebo-controlled, six-period crossover study to determine whether the abuse potential of NRP104 (50, 100, and 150 mg) is less than that of immediate release d-amphetamine sulfate 40 mg and diethylpropion hydrochloride 200 mg in 36 patients with a diagnosis of stimulant abuse aged 18 to 55

4.3 Review Strategy

A listing of the items examined during the course of this review is provided in Table 4.3.1. The study reports for the Phase 1 studies (102, 101, 104, 106, 103, and 302), the ongoing study (302), and the abuse studies (A01, A02, and A03) were examined for major safety findings only.

TABLE 4.3.1: ITEMS UTILIZED IN THE REVIEW

Submission Date	Items Reviewed
December 6, 2005	Clinical Study Reports: Studies 201 and 301 Proposed Labeling Financial Disclosure Certification Application Summary Case Report Tabulations (.xpt files) Case Report Forms
March 16, 2006	General Correspondence

April 11, 2006	4-Month Safety Update Integrated Summary Case Report Tabulations Case Report Forms Interim Clinical Study Report: 302
June 9, 2006	Clinical Study Report: A03
June 16, 2006	Amendment to a Pending Application: Updated Draft and Annotated Labeling Text
June 29, 2006	Response to FDA Request

4.4 Data Quality and Integrity

The efficacy data from the two positive trials were examined by the statistical reviewer, Yeh-Fong Chen, Ph.D., and there were no outliers or sites identified that were felt to be driving the efficacy results. The Division of Scientific Investigations (DSI) chose 3 U.S. sites from the studies 201 and 301 for inspection: Dr. Frank Lopez, Dr. Ann Childress, and Dr. [redacted] This was based on the number of enrollments and the last date of inspection. Results of the DSI inspections are described in section 3.4.

I conducted an audit of adverse event safety data by comparing Case Report Forms (CRF's) and adverse event line listings for consistency of adverse event information across these two documents in a random sample of 2 patients. No Narrative Summaries were provided. Results are described in section 7.2.7 of this review.

4.5 Compliance with Good Clinical Practices

Studies 201 and 301 were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) according to the International Conference on Harmonization (ICH) guidelines.

4.6 Financial Disclosures

For purposes of this NDA supplement, both studies (201 and 301) are considered "covered clinical stud[ies]" in accordance with 21 CFR 54.2 (e).

Among the clinical investigators in this study, one was identified by New River as having financial arrangements that require disclosure:

[redacted] investigator at study site [redacted], held significant equity interest (in excess of $50,000) with New River Pharmaceuticals, Inc. It is unlikely that

these arrangements biased the study results since this was a double-blind trial and her site contributed only [redacted] patients (about 5%) of the [redacted] patients in the study.

5 CLINICAL PHARMACOLOGY

Please note that a Clinical Pharmacology and Biopharmaceutics review was not available at the time of completion of this review, and the information below was obtained from the sponsor's Summary of Clinical Pharmacology Studies.

5.1 Pharmacokinetics

NRP104 is not metabolized by the liver to form either amphetamine or amphetamine-derived metabolites and there was no significant inhibition by NRP104 of any of the cytochrome P450 isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. There was essentially no hydrolysis of NRP104 by any of the enzymes tested. Although there were trace amounts of d-amphetamine after hydrolysis by Pancreatin and Endopeptidase Lys-C, these were <1% after 4 hours.

After oral administration of ^{14}C NRP104, there was a minimal amount of NRP104 that was essentially cleared by 8 hours after dosing. The majority of radioactivity in the plasma was associated with d-amphetamine and some radioactivity was associated with other moieties, most likely amphetamine metabolites. Essentially all of the ^{14}C was excreted in the urine with trace amount in the feces and excretion was complete within 72 to 96 hours, consistent with the $t_{1/2}$ of d-amphetamine. Approximately 2% of the administered dose of ^{14}C was recovered in the urine as NRP104 and 40% was recovered as amphetamine.

The pharmacokinetics of d-amphetamine was linear over doses of NRP104 ranging from 30 mg to 70 mg in children with ADHD. In healthy adults with histories of stimulant abuse, the pharmacokinetics of d-amphetamine were linear over doses ranging from 30 mg to 130 mg but substantially attenuated between doses of 130 to 150 mg, which the sponsor asserts is consistent with the hydrolysis of NRP104 to d-amphetamine.

Plasma d-amphetamine concentrations reached a three to four fold lower C_{max} at a later T_{max} after intravenous administration of NRP104 than compared to the equivalent dose of d-amphetamine sulfate.

Overall exposure, based on AUC_{∞}, was comparable between 25 mg of NRP104 and 10 mg of d-amphetamine sulfate and 50 mg of NRP104 and 20 mg of d-amphetamine sulfate. The steady-state pharmacokinetics of d-amphetamine after administration of 70 mg NRP104 once daily for 7 days were consistent with those from a single dose.

[3] Number of patients based on Efficacy ITT

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 21, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for lisdexamfetamine (NRP-104) capsules for the treatment of attention deficit hyperactivity disorder (ADHD)

TO: File NDA 21-977
[Note: This overview should be filed with the 12-22-06 response to our 12-21-06 approvable letter.]

[Note: See my approvable memos dated 9-28-06 and 12-20-06 and Dr. Khin's approval memo dated 2-16-07 for background information on this NDA.]

We issued 2 approvable letters for this application (10-6-06 and 12-21-06). The obstacles precluding a final approval action in the last review cycle were predominantly CMC, i.e., there were still concerns about the quality of drug substance coming from the [redacted] facility, and it was not possible to establish a retest period for drug substance batches or to establish an expiry. These concerns have now been resolved and CMC has recommended an approval action.

There were a few relatively minor clinical labeling issues, and these have also been resolved. In the meantime, we have asked the sponsor to adopt a medication guide that has been developed for other stimulant products, and they have agreed to this. The sponsor has agreed to several minor labeling changes regarding biopharmaceutical issues, and they have agreed to the dissolution specifications proposed by the OCP group. We reached final agreement with the sponsor on labeling and the medguide on 2-16-07.

The sponsor has agreed to a phase 4 commitment to conduct a clinical study in adolescents with ADHD and submit the results within 3 years.

In the draft approval letter we have asked them to make a minor change in the container label to make it easier to read, and we have reminded them that DEA will make a final scheduling determination. We have also reminded them of their commitment not to market this product until scheduling is finalized.

I want to mention for the record one other issue that has been raised during the process of reviewing this new drug. This concern was raised in the form of e-mails to me by a Dr. [redacted]

[redacted], a physician at [redacted]. These e-mails were sent on 10-10-06, 10-31-06, and 2-17-07. I responded to the first e-mail by simply informing Dr. [redacted] that any information pertinent to a pending application was privileged and that I could not discuss any of these matters with him. However, I did share his e-mails with other review staff. His most recent e-mail (2-17-07) was directed to Dr. Von Eschenbach (and copied to me), and in essence, it raises a theoretical concern that there may be a subgroup of children who are unable to cleave L-lysine from the prodrug, lisdexamfetamine, and, they therefore might develop supratherapeutic levels of lisdexamfetamine. Dr. [redacted] suggests that we should have required a very large population to be exposed to this prodrug before approval, presumably to rule out this possibility. He suggests that we might expect "reports of sudden, arrhythmic deaths" once this drug is approved, presumably due to these supratherapeutic levels. My view is that Dr. [redacted] thinking is flawed, since lisdexamfetamine does not, to my knowledge, have any sympathomimetic activity. It is highly speculative to suggest in the first place that there is such a subgroup of patients, but even if there were, it would not be expected that patients having higher than expected levels of lisdexamfetamine would be at risk of sympathomimetic toxicity. I scheduled a meeting with other review staff on 2-20-07 to further discuss this matter, and there was unanimous agreement that there is no basis for Dr. [redacted] expressed concern. The meeting was attended by representatives of CMC (Drs. Oliver, Sood, and Soldatova), pharmacology (Drs. Rosloff and Elayan), OCP (Drs. Baweja and Jackson), and clinical (Dr. Mathis and myself). The following observations were made at this meeting:

-Contrary to Dr. [redacted] assertions, there is remarkably little pharmacokinetic variability with lisdexamfetamine, i.e., an argument against the possibility of genetic variability regarding the cleavage of lysine.

-What genetic variability there is with drug metabolism is seen mostly with oxidative metabolism (i.e., the CYP-450 system), and not with enzymative cleavage which is what underlies the conversion of this prodrug into d-amphetamine. In fact, there are several different enzymes that facilitate this cleavage, which argues against the possibility of genetic differences in any one enzyme resulting in intersubject variability.

-Dr. [redacted] is incorrect in his assertion that it is gastric acid hydrolysis that underlies the lysine cleavage. Rather, as noted, it is enzymatic cleavage that underlies this conversion.

-The other pertinent issue is that Dr. [redacted] is incorrect in his assumption that intact lisdexamfetamine is active. All the available evidence indicates that it is inactive, including both in vitro assays and in vivo animal data. In vitro assays showed that lisdexamfetamine has no activity at DA, NE, and a variety of other receptors. In vivo assays suggest that all the activity of orally administered lisdexamfetamine is due to the d-amphetamine that is released from the prodrug. IV administration of lisdexamfetamine results in increased levels of lisdexamfetamine and decreased levels of d-amphetamine, compared to oral administration of lisdexamfetamine, with a resultant decrease in amphetamine-like activity, because the lisdexamfetamine is without activity. Consequently, Dr. [redacted] expressed concern about toxicity of lisdexamfetamine is completely groundless.

New River Pharmaceuticals, Inc. has, in my view, submitted sufficient data to support the conclusion that NRP1-4 is effective and acceptably safe in the treatment of ADHD. It is my view that all remaining issues have been addressed, including agreement on labeling. Therefore, I recommend that we proceed with a final approval action. Of course, once approved, this

product cannot be marketed until DEA makes a final determination about the controlled substances classification.

cc:
Orig NDA 21-977
HFD-130
ODE-I/RTemple
HFD-130/TLaughren/MMathis/NKhin/MChuen/FCurtis

DOC: Lisdexamfetamine_Laughren_AP Memo.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

HFA-305

JUL 26 1989

John D. Seigfried, M.D.
Executive Director
Regulatory Affairs
McNeil Pharmaceutical
Spring House, PA 19977-0776

Re: 87P-0339/CP
87P-0339/PSA001

Dear Sir:

This is in response to your petition to the Food and Drug Administration (FDA) seeking 5 years of exclusive marketing under section 505(j)(4)(D)(ii) and (c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act (the act) for the product haloperidol decanoate, described in new drug application 18-701 and approved for marketing on January 14, 1986. The citizen petition (87P-0339/CP) was dated October 2, 1987, and filed by our Dockets Management Branch on October 6, 1987. The citizen petition requests that the agency reconsider its determination that the exclusive marketing period FDA accorded haloperidol decanoate extended only to January 14, 1989, which is 3 years from the date of NDA approval, under section 505(c)(3)(D)(iii) and (j)(4)(D)(iii) of the act. The petition argues that haloperidol decanoate should have been awarded 5 years of exclusive marketing under section 505(c)(3)(D)(ii) and (j)(4)(D)(ii). A supplement was filed March 2, 1988. This supplement was, in part, in response to FDA's decision on Abbott Laboratories' citizen petition requesting a longer period of exclusivity for the drug Depakote (Docket No. 86P-0367/CP), which addressed issues similar to those dealt with in your petition. Abbott Laboratories brought suit challenging FDA's decision on the citizen petition and summary judgment was entered against Abbott. Abbott Laboratories v. Young, 691 F. Supp. 462 (D.D.C. 1988). You submitted a second supplement dated September 30, 1988. This second supplement relies on the court's opinion in Abbott Laboratories v. Young and posits a new description of the drug. You submitted a third supplement, dated March 27, 1989, and filed March 29, 1989, drawing the agency's attention to the decision in Glaxo Operations UK Ltd. v. Quigg, Civil No. 88-1487-A (E.D. Va. Feb. 17, 1989) and enclosing a copy of the court's opinion.

McNeil also submitted a petition, dated January 12, 1989, requesting that the agency stay the approval of any abbreviated new drug applications (ANDA's) and "paper" new drug applications (NDA's) for haloperidol decanoate, pending the decision on the exclusivity petition, and for 30 days after the decision if the exclusivity petition is denied.

We have carefully reconsidered our decision on the period of exclusivity to which haloperidol decanoate is entitled in light of all of the petition's arguments. We again find that haloperidol decanoate is entitled to 3 years of exclusivity, but does not meet the requirements that entitle a product to 5 years of exclusivity. We therefore deny the petition.

D-0339

D-1001

FDA's decision on this petition is consistent with previous agency decisions on similar issues. It is also consistent with the court's opinion in Abbott Laboratories v. Young. See court's decision denying FDA's motion to alter the opinion decided June 22, 1989, at 9-10. The agency is aware of the opinion in Glaxo v. Quigg, but is not bound by that decision which concerns provisions of Title II of the Drug Price Competition and Patent Term Restoration Act of 1984, rather than the provisions of Title I at issue in this petition. We also deny the petition requesting that we stay approval of ANDA's and "paper" NDA's for haloperidol decanoate.

BACKGROUND

The exclusivity provisions at issue in the petition are contained in Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Amendments). These provisions limit, in certain circumstances, the date on which approval of a generic drug's ANDA (or section 505(b)(2) application) may be made effective. In FDA's February 11, 1988, response to a citizen petition submitted by Abbott Laboratories (Docket No. 86P-0367/CP) in which Abbott sought 10 years exclusivity for a product to which FDA granted 2 years, FDA set forth the relevant provisions of the 1984 Amendments and their legislative history. FDA will not repeat that discussion here.

The 3-year exclusivity provision is contained in paragraphs (c)(3)(D)(iii) and (j)(4)(D)(iii) of section 505. Those paragraphs prohibit the agency from making an approval of an ANDA or a section 505(b)(2) application for a generic copy of an approved drug effective when that approved "drug ... includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of the enactment of this clause and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant..." This provision, which applies to drugs that are not new chemical entities, is applicable to haloperidol decanoate because the drug was approved on January 14, 1986, after the enactment date of the amendments [September 24, 1984]; the drug includes haloperidol decanoate, an ester of a previously approved active ingredient; and tests other than bioavailability studies were essential to the drug's approval.

The 5-year exclusivity provision is contained in paragraphs (c)(3)(D)(ii) and (j)(4)(D)(ii) of section 505. (The agency will hereinafter refer only to section 505(j)(4)(D)(ii) for brevity.) Those paragraphs prohibit the agency from making effective for 5 years an approval of an ANDA or a section 505(b)(2) application for a generic copy of a drug that was approved after September 24, 1984, and contains "no active ingredient (including any ester or salt of the active ingredient)" previously

approved in an application under section 505(b). This 5-year period of exclusivity applies to drugs that are "new chemical entities." The agency has considered the petitioner's arguments and concluded that the 5-year provision does not apply to haloperidol decanoate because it is not a new chemical entity but an ester of the previously approved ingredient haloperidol.

THE PETITIONER'S INTERPRETATION OF THE STATUTE IS INCORRECT

The petitioner argues that under section 505(j)(4)(D)(ii) of the act, haloperidol decanoate is entitled to 5 years of exclusivity because "neither the active ingredient (haloperidol decanoate) nor any salt or ester of the active ingredient has ever been approved in any other NDA." FDA has previously considered and rejected this interpretation of the exclusivity provision in the agency's response to Abbott Laboratories' citizen petition, supra. The discussion in FDA's response will not be repeated in detail here. A copy of FDA's response to Abbott's petition is attached. FDA's decision that a salt of a previously approved drug was not entitled to 10 years exclusivity was upheld in Abbott Laboratories v. Young, supra.

Briefly, FDA believes that the petitioner's interpretation of section 505(j)(4)(D)(ii) is incorrect, in that it relies on reading into the provision language that is not there, thus changing the meaning of the provision. The words "neither" and "nor," which do not appear in the statute, change the meaning of the provision, which actually reads, as just noted, "... a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been ... [previously approved]." FDA interprets Congress' use of the phrase "including any ester or salt" to mean that esters and salts are intended not as an exhaustive list but as examples of the types of minor variations in chemical structure that Congress did not intend to reward with exclusivity. Thus, FDA believes that Congress intended the phrase "no active ingredient (including any ester or salt)," in its entirety, to refer to the active moiety of a drug.

This interpretation of the phrase "active ingredient (including any ester or salt of the active ingredient)" as meaning "active moiety" is consistent with the legislative history of the 1984 Amendments and with FDA's longstanding interpretation of similar terms. Congress repeatedly described the types of drugs for which 5 years of exclusivity would be available as "new chemical entities." (See, e.g., 130 Cong. Rec. H9113 (daily ed. Sept. 6, 1984) (statement of Rep. Waxman); 130 Cong. Rec. S10504 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch).)

Under FDA's longstanding system for classifying drugs, a new chemical entity is one containing a never-before-approved active moiety. Such drugs are classified as Type I drugs. A new ester or salt of a

previously approved ingredient is not considered a new molecular entity and is classified as a Type II drug.1/ The legislative history of Title II of the 1984 Amendments shows that Congress was aware of and intended to adopt FDA's definition of a Type 1 new chemical entity in using the phrase "active ingredient ... including any salt or ester ...". (See H.R. Rep. No. 857, Part 1, 98th Cong., 2d Sess. 37-8 (1984).) This language in Title II is virtually identical to that used in Title I's section 505(j)(4)(D)(ii). Thus, FDA concludes that in using the phrase "active ingredient (including any ester or salt of the active ingredient)" in section 505(j)(4)(D)(ii), Congress intended to refer to new active moieties and to confer 5 years of exclusivity only on never-before-approved active moieties.

If the phrase "active ingredient (including any ester or salt)" is interpreted as petitioner suggests, application of section 505(j)(4)(D)(ii) would result in granting 5 years of exclusivity to salts and esters of previously approved ingredients. Because salts and esters of previously approved ingredients are not "Type 1" new chemical entities as that term was understood at the time the 1984 Amendments were passed, petitioner's construction would be inconsistent with the purpose of the 5-year exclusivity provision, which, as expressed by Congress, was to reward new chemical entities.

Moreover, petitioner's construction of the statute produces the absurd result that if a given chemical compound is marketed first, followed by its ester, both are "new chemical entities" and both get the maximum period of exclusivity, whereas if the ester is marketed first, followed by one of the ester's constituent compounds, only the ester is a "new chemical entity" and only the ester gets exclusivity. Thus, under petitioner's construction, "new chemical entity" is defined not by the "newness" of a compound or the significance of its innovation but by the order in which it is marketed. There is no rational basis for this differential treatment; there is no difference in the degree of innovation, cost, or therapeutic benefit associated with developing an

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1/ FDA's IND/NDA Classification System, which existed at the time the 1984 Amendments were drafted, classifies drugs into the following chemical types:
Type 1 - New molecular entity - i.e., the active moiety is not yet marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product.
Type 2 - New salt - i.e., the active moiety is marketed in the United States by the same or another manufacturer but the particular salt, ester, or derivative is not yet marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product.

ester after one of its constituent compounds as opposed to developing the constituent compounds after the ester. Also, many compounds would fall within both the 5-year exclusivity provision and the 3-year provision, two complementary provisions whose coverage is intended to be mutually exclusive. Sections 505(j)(4)(D)(iii) and (iv) provide 3 years of exclusivity to a drug that "includes an active ingredient (including any ester or salt of the active ingredient) that has been [previously] approved," but that required the completion of new clinical studies for approval. These provisions were intended to complement the provisions applicable to new chemical entities by providing a lesser period of exclusivity to products, like haloperidol decanoate, that are not new chemical entities because they "include ... an ester or salt ... of an active ingredient that has been previously approved," but that deserve some reward because they required certain additional studies, and thus substantial expense on the part of the manufacturer, before they could be marketed. See, e.g., 130th Cong. Rec. S10504 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch).2/ Petitioner's argument that haloperidol decanoate falls within section 505(j)(4)(D)(ii), if correct, would require the agency to presume that Congress intended the coverage of paragraphs (ii) and (iii) to overlap and thus to have intended that a single compound would be considered both a "new chemical entity" and a "non-new-chemical-entity." FDA does not believe that such a presumption is sound, in light of the legislative history contradicting such an anomalous result and the absence of any statutory guidance on which of the two paragraphs to apply to a compound that appears to fall within both provisions.

2/ There is to be a prospective 5-year waiting period for filing of ANDA's following approval by FDA of a new chemical entity new drug application [NDA]. For all other NDA's involving clinical tests, there will be a 3-year period during which no ANDA approval may be made effective. This protects products whose development has taken much time and money in FDA testing and review, but which have little for [sic] no patent life left when they are finally allowed on the market.

Further, the 10-year ANDA moratorium for products approved between January 1, 1982, and the date of enactment is supplemented by a similar provision for 2 years for non-new-chemical-entity drugs.

130th Cong. Rec. S10504 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch). (Emphasis added.)

The Supreme Court has repeatedly recognized that a construction of a statute that produces absurd results or results plainly at odds with Congress' purpose may be rejected, even if based on the statute's literal language. (See, e.g., Bob Jones University v. United States, 461 U.S. 574, 586 (1983); United States v. American Trucking Ass'ns, 310 U.S. 534, 543-44 (1940).) FDA is therefore not required to adopt petitioner's construction of the phrase "active ingredient (including any ester or salt of the active ingredient)."

FDA concludes that its interpretation of the 5-year exclusivity provision is more consistent with the language and purpose of that provision than petitioner's reading of that provision. Accordingly, a product containing an ester of an active ingredient contained in a previously approved product is not entitled to 5 years of exclusivity.

Petitioner also argues that its product is entitled to 5 years of exclusivity because the agency must give the term "active ingredient" the same meaning when interpreting different portions of the act but has defined "active ingredient" as the ingredient present in the final dosage form of a drug product for purposes of section 505(j)(2)(A). FDA's reasons for rejecting this argument are set forth in the agency's response to Abbott Laboratories' citizen petition. FDA has not defined the term "active ingredient" differently in two different provisions of the act; the agency has defined the term "active ingredient" differently from the phrase "no active ingredient (including any ester or salt of the active ingredient)." Moreover, the law is clear that the same word need not be defined the same way in different portions of a statute if doing so would frustrate legislative intent. Helvering v. Stockholms Enskilda Bank, 293 U.S. 84, 86-88 (1934). The competing legislative purposes served by the ANDA application provisions on the one hand, and the exclusivity provisions on the other, would be thwarted by equating the term "same active ingredient" in the ANDA provisions with the phrase "active ingredient (including any ester or salt of the active ingredient)" in the exclusivity provisions. A narrow interpretation of the requirement in the ANDA provisions that a generic drug have the "same active ingredient" as the listed drug is necessary to carry out Congress' intent in enacting the public health-oriented ANDA provisions of the

act: to provide the American public with a supply of generic drugs that are as safe and effective as their brand-name counterparts.3/ A different interpretation of the phrase "no active ingredient (including any ester or salt of the active ingredient)," on the other hand, i.e., one that restricts exclusivity to new active moieties, is necessary to carry out Congress' intent in enacting the economically oriented exclusivity provisions: to provide significant incentives for "new chemical entities" but not for "minor changes in some chemical entity that has already been approved." (See 130th Cong. Rec. H9124 (daily ed. Sept. 6, 1984) (statement of Rep. Waxman).)

Moreover, FDA's construction of the two different phrases is consistent with the agency's longstanding interpretations of the terms "active ingredient" and "new chemical [molecular] entity," terms that were well-understood and adopted by Congress in the ANDA and exclusivity provisions of the 1984 Amendments. Because of differences in local toxicity and rate of absorption that can result from the use of a new

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3/ Section 505(j) of the Act, under which ANDA's are approved, specifically prohibits FDA from requiring tests (other than bioequivalence tests) on a proposed generic product if the product contains the "same active ingredient" as the approved drug. Section 505(j)(2)(A). Bioequivalence tests are not capable of detecting all medically significant differences between ingredients and their salts and esters, e.g., differences in local toxicity. If "same active ingredient" was interpreted as "same active moiety" for purposes of section 505(j)(2)(A), FDA would not have authority to require those tests necessary to determine whether a new salt or ester was as safe and effective as the approved drug. Moreover, section 505(j)(3) would provide no authority to disapprove an ANDA for a drug containing a new salt or ester of an approved ingredient even if there were insufficient evidence to assure the safety or effectiveness of the variation. Thus, FDA could be required to approve an ANDA for a never-before-approved salt or ester of a previously approved drug, without assurance that the new salt or ester was as safe and effective as the approved drug.

salt or ester, FDA has consistently treated different salts or esters as different "active ingredients" for purposes of ANDA approval.[4/] FDA has also consistently defined Type I "new chemical entities" as products containing never-before-approved active moieties, and has consistently treated new salts and esters of previously approved ingredients as Type II non-new-chemical-entities. See footnote 1. See, e.g., H.R. Rep. 857, Part 1, 98th Cong., 2d Sess. 21, 23; H.R. Rep. No. 857, Part 1, supra, at 37-8, reprinted in 1984 U.S. CODE CONG. & AD. NEWS 2670-71.

Finally, equating the narrow definition of "active ingredient" from the ANDA provisions with the phrase "active ingredient (including any ester or salt of the active ingredient)" in the exclusivity provisions would produce absurd results. Eligibility for exclusivity would depend on the order in which compounds are marketed rather than on innovation. As noted above, the agency is not required to interpret the statute in a manner that produces results that are absurd or at odds with the legislative purpose.

4/ As described at length in various regulations and Federal Register notices, before the adoption of the 1984 Amendments a product was automatically eligible for approval in an ANDA only if it was "identical" to (or a "duplicate" of) an approved product, i.e., if it contained the same ingredient as the approved drug, in the same dosage form and same strength. See 21 CFR 314.55 (formerly § 314.2 (1983)); 48 FR 2751, 2753-4 (Jan. 21, 1983). A new salt or ester was not considered identical to the approved drug, but was instead considered a "similar or related" drug, which could not be approved under an ANDA without prior approval of a petition in which the applicant demonstrated that no new safety or effectiveness issues were raised by the variation in active ingredient. Id. Congress' adoption of FDA's policy on "similar and related products" is contained in section 505(j)(2)(C) of the act, which requires the submission of a petition to file an ANDA for a drug containing a variation of the active ingredient in the approved product. If "active ingredient" were defined as "active moiety" for purposes of section 505(j)(2)(A), a new salt or ester would be the "same active ingredient" and no petition would be required to permit submission of an ANDA for the product, contradicting a decade of agency policy.

PETITIONER'S ARGUMENTS IN THE ALTERNATIVE

The petition contends that FDA's requiring two adequate and well-controlled studies prior to approval and a Phase IV post-approval study is inconsistent with granting only 3 years of exclusivity. FDA cannot agree with this contention, which implies that a request for a particular amount of clinical data must lead to a grant of 5 year exclusivity. In fact, the statute presumes that 3-year exclusivity will be granted only if significant clinical studies are done. Specifically, the grant of 3 years of exclusivity requires "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." Section 505(c)(3)(D)(iii) and (j)(4)(D)(iii) of the act. Haloperidol decanoate is thus a prime example of a drug entitled to the intermediate period of exclusivity. The product contains a previously approved active moiety in an ester form, and much of the safety data for haloperidol is applicable to the new product (and need not be re-obtained) but the differences between the two drugs are significant enough to require clinical testing, other than bioavailability studies. If no clinical studies had been required for approval, haloperidol decanoate would not be entitled to any exclusivity under section 505(c)(3)(D) and (j)(4)(D) of the act. On the other hand the need for some clinical data does not cause the product to be a new chemical entity, which is the only kind of new drug entitled to 5 years of exclusivity.

Petitioner in its September 30, 1988, amendment puts forth the position that, under the rules of chemical nomenclature, haloperidol decanoate is not the decanoate ester of Haloperidol but rather an ester of decanoic acid.

FDA has not made any determination on whether, under rules of chemical nomenclature, haloperidol decanoate is properly denominated an ester of decanoic acid because even if it is an ester of decanoic acid, it is also an ester of haloperidol. Two compounds are required to form an ester; one an acid, the other a base (usually an alcohol). The active moiety of a drug can be either an acid or a base. In the present case, haloperidol decanoate is formed by the combination of haloperidol, the active moiety, and decanoic acid. McNeil argues that haloperidol decanoate must be considered the ester of decanoic acid rather than the ester of haloperidol, even though decanoic acid does not contribute to the intended therapeutic effect of the drug.

General usage by FDA and within the pharmaceutical industry is, however, to describe any drug that contains an esterified form of a previously approved active moiety as an ester of the approved active moiety, regardless of whether the approved moiety is an acid or a base. The general acceptance of this broad use of the term "ester" is demonstrated

by McNeil's own labeling for Haloperidol decanoate, which states that "HALDOL^R (haloperidol) Decanoate is the decanoate ester of the butyrophenone, HALDOL haloperidol." (Copy attached.) Further evidence of the universality of this usage is found on page 3 of your October 2, 1987, petition, which states that "[i]t [haloperidol decanoate] is the decanoate ester of haloperidol ...." FDA finds it noteworthy that, apparently, you did not consider haloperidol decanoate to be the ester of decanoic acid rather than the ester of haloperidol at any time during the review of your NDA and indeed not until September 1988, almost 1 year after the submission of your original petition.

FDA, too, has traditionally followed this usage, and has consistently classified esterified forms of previously approved alcohol compounds, like haloperidol decanoate, as Type II esters of the alcohol, when classifying new drugs under FDA's IND/NDA Classification System, which predates the drafting of the 1984 Amendments. This broad use of term "ester" is thus the use with which Congress was familiar when it enacted the Amendments. The class of esters in which the active moiety is contained in the acid is small compared to the class of drugs in which the active moiety is contained in the alcohol. If Congress had intended to differentiate and award exclusivity only to this small subset of esters, the agency must presume that it would have expressly and unequivocally done so, rather than relying on a usage that was nonstandard in the agency and the industry affected by the legislation.

The petition also argues, in the alternative, that haloperidol decanoate has a different active moiety than haloperidol. FDA does not agree. The active moiety (i.e., the molecule or ion, excluding those appended portions that cause it to be an ester, a salt, or other noncovalent derivative, such as a complex, chelate, or clathrate, responsible for the physiological or pharmacological action of the drug substance) in haloperidol decanoate is the same as that of haloperidol. The minor change in chemical structure between haloperidol and its decanoate ester did not result in a new active moiety. The only significant pharmacological difference between the two drugs is the increased duration of action for haloperidol decanoate.

Statements made by McNeil in the labeling for haloperidol decanoate confirm that haloperidol and haloperidol decanoate have the same active moiety: "HALDOL (haloperidol) Decanoate is a long-acting form of HALDOL [McNeil's tradename for haloperidol]. The basic effects of HALDOL Decanoate are no different from those of HALDOL with the exception of duration of action.... Since the pharmacological and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified only to reflect the prolonged action."

Finally, in your supplement dated September 10, 1988, you contend that if FDA interprets section 505(j)(4)(D)(ii) as providing exclusivity only for "new active moieties," the agency has inconsistently applied this interpretation. In support of this contention, you cite three H2 blockers that were each treated as new chemical entities (cimetidine, ranitidine, and famotidine); you claim that these drugs in fact contain the same "active moiety."

Although the drugs you have cited contain molecules with a common grouping of atoms that allows them to bind to the histamine receptor, a grouping that could be called the "active site" of the molecule, these drugs do not share the same "active moiety," as FDA has consistently defined that term. As noted above, the "active moiety" of a drug is the molecule or ion responsible for the pharmacological action of the drug, excluding only those appended portions that cause it to be an ester or a salt or other non-covalent derivative. Although the "active site" of the molecule may be responsible for a specific pharmacological action of the drug, other portions of the active moiety affect the activity of the drug, e.g., by affecting its distribution within the body, its metabolism, its excretion, or its toxicity. The "active moiety" of a drug thus consists of both the active site, if that is known, and those other portions of the molecule affecting the drug's activity that remain after absorption of the drug into the systemic circulation and after exclusion of the appended portions that cause the molecule to be an ester salt or other noncovalent derivative.

FDA's definition of "active moiety" as encompassing both the active site and other covalently bound portions of the molecule reflects concepts that are well-recognized to anyone familiar with pharmaceutical development. It has been FDA's longstanding experience that even minor covalent structural changes are capable of producing not only major changes in the activity of a drug but changes that are not readily predicted. Because of their potential significance, FDA has always identified changes in covalent structure, including minor changes (e.g., adding a hydroxyl group or substituting a methyl side-chain for an ethyl group), as sufficient to create a new "active moiety," and thereby to create a new chemical entity.

The potential significance of modifications in covalent structure, even where previously approved drugs contain the same "active site," is reflected in the amount and kind of data required for approval of such changes. Such a change requires submission of an amount of data comparable to that required for an entirely new molecule. This amount of data was required for both ranitidine and famotidine, even though each shared the same "active site" as previously approved cimetidine. Each drug was studied in thousands of patients and had to be demonstrated to

be effective and safe entirely without reference to, or reliance on, information related to cimetidine. Indeed, studies have revealed numerous differences between cimetidine, ranitidine, and famotidine; these differences should not be surprising in view of the substantial differences in these molecules apart from their common portion.

In contrast to most changes in the covalent structure of a molecule, the formation of a salt or a complex, or of an ester, is not intended to, and generally cannot, alter the basic pharmacologic or toxicologic properties of the molecule (except for possible local toxicity). The formation of salts and esters (or the elimination of those appended portions to form a "base") cannot generally alter the basic pharmacologic and systemic toxicologic effects because formation of salts and esters does not alter the molecule or ion that is actually absorbed into the systemic circulation and goes to the site of drug action.5/

Because new esters and salts and other noncovalent derivatives generally produce only changes in rate of absorption or in local toxicity, their approval does not require the amount of safety and effectiveness data required for a new active moiety (whether the new moiety is an entirely new molecule or a change in the covalent structure of a known molecule). The fact that the same active moiety circulates and travels to the site of drug action, regardless of whether the drug is administered in the form of a salt, ester, or base, precludes differences in the basic pharmacologic or toxicologic properties of the drug. The data required for an approval of a new salt or ester or base are thus generally only

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5/ Although forming an ester causes a change in the covalent structure of the molecule, formation of an ester is more analogous to changes in noncovalent structures than to other changes in covalent structure. Portions of a molecule that are not covalently bound to the molecule, such as those portions that cause a drug to be a salt or complex, are designed to be separated from the "active moiety" before the drug is absorbed into the circulation. These noncovalently bound portions do not travel to, or act on, the site of drug action. Covalently bound portions, on the other hand, generally remain part of the active moiety and travel to the site of drug action. The formation of an ester, unlike other covalently bound groups, is in almost all cases designed to be removed before, or just after, absorption by gut or blood esterases; at that point the ester portion is cleaved from the "active moiety," and only the active moiety travels to, and acts on, the receptor site.

those required to answer any questions related to different rates of absorption or on local toxicity. While the applicant is generally not required to repeat tests on the basic safety of the drug, the change in rate of absorption can raise the question of whether effectiveness persists and at what dose it persists, so that new clinical studies may be needed.

In conclusion, for the reasons explained above, we find that the citizen petition has not shown that haloperidol decanoate qualifies for 5 years of exclusivity and we therefore deny the citizen petition.

REQUEST FOR STAY

In a "Petition for Stay of Action" submitted on January 17, 1989, McNeil also requested that FDA stay the effective date of any approvals of ANDA's or paper NDA's referring to NDA No. 18-701 (haloperidol decanoate), pending FDA's decision on the citizen petition seeking 5-years of exclusivity for haloperidol decanoate, and for 30 days thereafter in the event that the petition is denied. No ANDA's or paper NDA's referring to haloperidol decanoate have been approved to date; that part of the petition requesting a stay pending decision on the citizen petition is therefore moot, and FDA will respond herein only to that part of the petition for stay requesting that FDA delay the effective date of any such ANDA's or paper NDA's for 30 days following denial of the citizen petition.

FDA is required to make effective immediately an application submitted under section 505(b)(2) or (j) of the act that satisfies the approval requirements in section 505(c)(1) or (j)(3) unless the drug on which the application relies is entitled to a period of exclusivity that has not yet expired (section 505(c)(3)(D) and (j)(4)(D)), or the applicant has made a patent certification resulting in a delayed effective date (section 505(c)(3) and (j)(4)(B)). As explained above, FDA has concluded that haloperidol decanoate satisfied the statutory criteria for 3 years of exclusivity but not the criteria for 5 years. Because there are no listed patents on haloperidol decanoate and the 3-year period of exclusivity expired on January 14, 1989, FDA has no authority to grant a stay delaying the effective date of approval of any application for a generic version of haloperidol decanoate approved after January 14, 1989.

FDA's regulations require the Commissioner to grant a stay of action if all of the following conditions are met: (1) the petitioner will otherwise suffer irreparable injury, (2) the petitioner's case is not frivolous and is being pursued in good faith, (3) the petitioner has demonstrated sound public policy grounds supporting the stay, and (4) the delay resulting from the stay is not outweighed by public health or other interests. Petitioner asserts that these conditions are met but provides

no arguments or facts in support of its assertion, other than a reference to FDA's interim response to the citizen petition in which FDA stated that the petition raised complex questions regarding the agency's interpretation of the act. Because FDA has now reached a final determination on these questions, this argument no longer supports a stay. In any event, where Congress has not given FDA the authority to delay the effective dates of ANDA's or paper NDA's, granting a stay would exceed the agency's authority, and would thus be contrary to sound public policy and the public interest.

The conditions for granting a stay thus cannot be met under the circumstances presented. FDA is therefore denying petitioner's request that the effective date of approval of any ANDA's or paper NDA's be delayed for 30 days following the denial of the petition.

Sincerely yours,

Ronald G. Chesemore
Acting Associate Commissioner
for Regulatory Affairs

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT

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August 5, 1985

Frank E. Young, M.D.
Commissioner
Food and Drug Administration
HF-1
5600 Fishers Lane
Rockville, MD 20857

Re: Zenith Laboratories v. Heckler

Dear Commissioner Young:

It is my understanding that FDA has been sued in the United States District Court for the District of New Jersey by Zenith Laboratories regarding its petition to obtain three years of marketing exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Act) for its generic drug, Tolazamide. As Chairman of the Subcommittee on Health and the Environment, I was the original author of the Act and the principal sponsor of the legislation in the House of Representatives and now have legislative authority over the Act. Therefore, I am vitally concerned that the Act be implemented in accordance with the statutory language and Congressional intent.

I have reviewed the Zenith petition. Because the law suit is the first judicial test of the provision regarding three year market exclusivity, I want to communicate to you my view that the FDA's rejection of the Zenith petition is the result Congress intended under the Act. If you had granted the petition, you would have undermined Congress' resolution of one of the most contentious issues in the Act -- marketing exclusivity. I urge you to be vigorous in defending your decision.

Allow me to explain why your decision is consistent with Congressional intent.

As you know, section 505 (j)(4)(D) of the Federal Food, Drug and Cosmetic Act was added by the Act and contains several provisions for marketing exclusivity. The five year rule (section 505 (j)(4)(D)(ii)) for approval of new chemical entities and the three year rule (section 505 (j)(4)(D)(iii-iv)) for approval of certain non-new chemical entities are prospective in application and address the same concern. Congress wanted to assure that drug companies were rewarded for major innovations involving either a new drug or a new use for an already marketed drug by guaranteeing them a period of marketing exclusivity during which time they could recoup their developmental costs.

Our concern was that while the patent system usually provides sufficient rewards for innovation, there may be cases when inadequate patent protection would deter a company from attempting to discover and get approval for a new drug or a new use of a marketed drug. In these cases, e.g., expired or invalid patents, Congress wanted the innovator still to have an incentive to make breakthroughs that would benefit the public.

In establishing this new monopoly power, though, the Congress understood it would be depriving consumers of the benefits of price competition, so the provisions were carefully limited to new chemical entities, which by definition are innovative, and to those changes in already marketed drugs, such as a new use, which are important innovations. Congress also understood that the substantial economic rewards of the three year rule might well encourage drug companies to make minor and unimportant alterations in their marketed drugs or to conduct additional tests which they could claim provide important new information about a marketed drug. To avoid rewarding such behavior, the three year rule includes special criteria intended to restrict eligibility.

The eligibility criteria are that the drug company's application must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant..." There are several important aspects to these criteria. First, the investigations must be "clinical" studies and they must relate to efficacy. Congress wanted and required human efficacy testing. Therefore, we deliberately chose the term "clinical" because it is commonly understood under the Federal Food, Drug and Cosmetic Act to mean human studies. Congress imposed this requirement because human efficacy studies are the best indication that the new aspect of the marketed drug, which aspect is under testing, is an important new change in the marketed drug, such as a new use. Congress' specific exclusion of "bioavailability studies," which are also clinical (because they are done in humans), indicates our determination to limit eligibility to changes in a drug which are so significant that human efficacy studies are required before approval is possible. In using the word "clinical," Congress intentionally excluded all animal studies, regardless of the purpose for which they are performed.

Second, the human tests must be "new" and "conducted or sponsored by the applicant." Congress required that these human tests by the drug manufacturer be done solely for the purpose of seeking FDA approval of the new aspect of the marketed drug. We did not want companies simply to collect information from the literature, or buy the results of older tests or tests done for other reasons and submit them to the agency.

Third, the human tests must be "essential to the approval of the application." In other words, FDA could not approve the application unless the human tests were conducted because, without these new clinical trials, FDA would not have sufficient information to determine

that the new aspect of the marketed drug is safe and effective. In drafting this language, we explored several options: "essential," "pivotal," "without which the application could not be approved." We settled on "essential" because we thought it best communicated the absolute necessity of human tests to the approval of a new aspect of a marketed drug.

In summary, the Congress built in these criteria so that the economic benefits or the three year rule would be available only for those aspects of marketed drugs so new that FDA could not know of their safety and effectiveness unless human tests were conducted. With these criteria, Congress felt reasonably certain that eligibility would be restricted to those aspects of marketed drugs which provide important innovations for consumers. Congress did not intend to provide eligibility under the Act for human bioavailability studies or animal tests that provide additional evidence of safety regarding current uses of a drug. Such studies certainly do provide important consumer benefits. But, Congress did not believe that they provided benefits that justified the grant of monopoly power to a drug manufacturer. The award of substantial economic benefits to the manufacturer is warranted only if the public has access to an important innovation, i.e., a new drug or a new use for a current drug.

The problem with Zenith's application is that Zenith did nothing innovative. It has sought approval for the same use of the same drug already on the market. The costs it incurred were of the type routinely required for generic drugs to get FDA approval before passage of the Act and were not related to a significant new use or some other significant improvement in the drug. Zenith's work did provide new information to FDA with respect to the current use of the drug. For this, it should be granted approval to market the drug. However, this approval should not carry exclusivity. Zenith did not come to FDA with the type of innovation contemplated in the Act.

As further confirmation of Congress' intent, I would also remind you of the legislative history regarding the words in section 505(j)(4)(D)(iii) and (iv) which are at issue in the Zenith petition. Because of the particular legislative procedure we used in passing the Act, there was no conference between the two Houses, nor was there a Senate Committee Report on the Act. However, the manner in which this language entered the Act clearly reveals Congress' intent.

The original version of the Act was contained in H.R. 3605, as reported by the Energy and Commerce Committee (see Report Number 98-857) and in S. 2748. Subsequently, as negotiations proceeded between Senator Hatch, representatives of the brand name manufacturers, representatives of the generic drug manufacturers and me, the Senate introduced a new version of the bill, S. 2926, on August 9, 1984. This new version contained the first mention of the three year rule. (In section 101 of the bill, see section 505 (j)(4)(D)(iii).) It did not contain the following language now in the Act: "and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant."

I raised objections to the breadth of eligibility for the three year rule in S. 2926, so negotiations continued that day, August 9, 1984, between the same parties. On August 10, 1984, when S. 2926 passed the Senate, section 505(j)(4)(D)(iii) had been split into two subparagraphs [(iii) and (iv)] and amended to include the following language: "and which contains reports of new clinical investigations (other than bioavailability studies) sponsored by the applicant."

The Senate-passed bill was sent to the House, and on September 6, 1984, the House began consideration of its version, H.R. 3605. Because I continued to have concerns about the language of subparagraphs (iii) and (iv) in the Senate-passed bill, I insisted on further changes. They were agreed to by all parties in the negotiations and were included in the House-passed bill. The amendment I offered to H.R. 3605 was the text of S. 2926, as amended by the Senate, with several changes. Regarding the language in question, my amendment added the phrase "essential to the approval of the application and conducted or...." With these amendments, the current text of section 505(j)(4)(D)(iii) and (iv) was established and passed by the House. The text of H.R. 3605, as amended, was then added to an unrelated Senate-passed bill, S. 1538, and returned to the Senate where it was passed and subsequently signed by the President.

I recount this history in such detail to indicate that this provision was the subject of constant negotiations, several amendments, and careful Congressional scrutiny. Congress knew exactly what it was passing and why. While the usual legislative history of a Conference Report is missing, I was intimately involved at every step and, with regard to the statutory language in question, sponsored the amendments that placed it in the Act.

In closing, I want to repeat that Congress' resolution of the differing viewpoints on marketing exclusivity was done with careful attention. If the restrictions imposed in eligibility are not followed as I explained them, then the specific intent of Congress and the statutory language will be severely undermined. I trust that you will do everything within your authority to see that the Act is so upheld.

Sincerely,

Henry A. Waxman

HENRY A. WAXMAN
Chairman, Subcommittee on
Health and the Environment

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 23, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for lisdexamfetamine (NRP-104) capsules for the treatment of attention deficit hyperactivity disorder (ADHD)

TO: File NDA 21-977
[Note: This overview should be filed with the 12-22-06 response to our 12-21-06 approvable letter.]

[Note: See my approvable memos dated 9-28-06 and 12-20-06, Dr. Khin's approval memo dated 2-16-07, and my original 2-21-07 approval memo for background information on this NDA.]

Two other issues were raise------t need to be addressed before final approval, both related to the concerns expressed by Dr. [redacted](see my 2-21-07 memo for my earlier comments on his concerns).

Dr. [redacted] expressed concern about the relatively small number of patients exposed to lisdexamfetamine in this development program (n=272). Although this is a small number compared to the typical NDA safety database, it is a reasonable number, in my view, given our knowledge that lisdexamfetamine is a prodrug for d-amphetamine, the active substance. We, of course, have substantial information to inform us about the safety profile of d-amphetamine. Furthermore, as I indicated in my 2-21-07 memo, we have substantial information to allow us to conclude that lisdexamfetamine does not have amphetamine-like activity, and, therefore, would not be capable of causing the cardiovascular adverse events that Dr. [redacted] seems to be concerned about. His concerns are conditioned upon his speculation that there is a subgroup of patients who cannot efficiently cleave lysine from lisdexamfetamine and who, therefore, might have higher levels of lisdexamfetamine than we have generally observed (all the data we have suggests that systemic exposure to lisdexamfetamine is very low following the recommended doses of this prodrug).

The second issue concerns the labeling for this prodrug. [redacted]. The best data we have regarding this issue are in vitro data that show that lisdexamfetamine does not bind at the DA and NE reuptake sites that underlie the sympathomimetic effects of amphetamines. Thus, on this basis, lisdexamfetamine would not be expected to have any amphetamine-like activity. As I

have noted in my 2-21-07 memo, in vivo animal data also suggest that lisdexamfetamine does not have amphetamine-like activity. We have added the following statement to labeling: "The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro." The sponsor has accepted this minor change to the label.

cc:
Orig NDA 21-977
HFD-130
ODE-I/RTemple
HFD-130/TLaughren/MMathis/NKhin/MChuen/FCurtis

DOC: Lisdexamfetamine_Laughren_AP2 Memo.doc

Shire

New River Press Releases

Shire and New River Pharmaceuticals Announce FDA Approval of the First and Only Stimulant Prodrug VYVANSETM (lisdexamfetamine dimesylate) as a Novel Treatment for ADHD

23 Feb 2007 - Shire and New River Pharmaceuticals Announce FDA Approval of the First and Only Stimulant Prodrug VYVANSE™ (lisdexamfetamine dimesylate) as a Novel Treatment for ADHD

Basingstoke, U.K., Philadelphia, PA and Radford, VA - FEBRUARY 23, 2007 - Shire plc (LSE: SHP, NASDAQ: SHPGY, TSX: SHQ) and its collaborative partner New River Pharmaceuticals Inc. (NASDAQ: NRPH) announced today that the U.S. Food and Drug Administration (FDA) has granted marketing approval for VYVANSE (lisdexamfetamine dimesylate, formerly known as NRP104), for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

On February 20, 2007 Shire and New River announced an agreement whereby Shire will acquire New River for approximately $2.6 billion in an all cash transaction unanimously recommended by the Boards of both companies. The transaction is the subject of another press release issued February 20, 2007.

VYVANSE is a prodrug that is therapeutically inactive until metabolized in the body. In clinical studies designed to measure duration of effect, VYVANSE provided significant efficacy compared to placebo for a full treatment day, up through and including 6:00 pm. Furthermore, when VYVANSE was administered orally and intravenously in two clinical human drug abuse studies, VYVANSE produced subjective responses on a scale of "Drug Liking Effects" (DLE) that were less than d-amphetamine at equivalent doses. DLE is used in clinical abuse studies to measure relative preference among known substance abusers.

"The FDA approval of VYVANSE is exciting news for Shire as well as for patients, their families, and healthcare providers as it's an important, novel approach for the treatment of ADHD," said Matthew Emmens, Shire Chief Executive Officer. "The label we received with the approval letter includes information about the extended duration of effect and abuse-related drug liking characteristics of VYVANSE which illustrate benefits that differentiate this compound from other ADHD medicines. The addition of VYVANSE to our ADHD portfolio reaffirms Shire's commitment to continue to address unmet medical needs and advance the science of ADHD treatment. Beginning with product launch in Q2 2007, Shire will make VYVANSE our top promotional priority within our ADHD portfolio."

Randal J. Kirk, New River's Chairman and Chief Executive Officer, remarked, "VYVANSE's approval signals a new era in the treatment of ADHD. Upon product launch, patients will have a novel treatment option combining the effectiveness of a stimulant - long considered the gold standard in ADHD medicines - with other potential benefits."

The FDA has proposed that VYVANSE be classified as a Schedule II controlled substance. This proposal was submitted to and accepted by the U.S. Drug Enforcement Administration (DEA). A final scheduling decision is expected from the DEA following a 30-day period for public comment. Once VYVANSE receives final scheduling designation, the label will be available. Pending final scheduling designation, product launch is anticipated in Q2 2007. VYVANSE will be available in three dosage strengths: 30 mg, 50 mg and 70 mg, all indicated for once-daily dosing.1

New River developed VYVANSE as a new ADHD medication designed to provide lower potential for abuse, in which d-amphetamine is covalently linked to l-lysine, a naturally occurring amino acid. The combination is rapidly absorbed from the gastrointestinal tract and converted to d-amphetamine, which is responsible for VYVANSE's activity.

Joseph Biederman, MD, director of Pediatric Psychopharmacology at Massachusetts General Hospital, was lead investigator on the pivotal clinical studies testing lisdexamfetamine dimesylate for the treatment of ADHD. These large multi-site studies showed that the drug significantly reduced ADHD symptoms throughout the day with a predictable tolerability profile. "Our studies showed that this next-generation stimulant medication's unique chemical profile offers an option for physicians and their patients in the treatment of ADHD, with outstanding efficacy and duration of action" said Dr. Biederman.

Additional information about VYVANSE and other Shire treatments for ADHD is available at www.ShireADHDTreatments.com.

VYVANSE Significantly Controls ADHD Symptoms

Data from phase II and phase III clinical trials demonstrated statistically significant improvements in ADHD symptoms for patients aged 6 to 12 years treated with VYVANSE compared to patients treated with placebo. These studies demonstrated that all doses of VYVANSE (30 mg, 50 mg and 70 mg) provided significant efficacy at all time points tested, including 6pm.2

In the phase II, analog classroom study, patients demonstrated significantly improved behavior when receiving either VYVANSE or ADDERALL XR® (mixed salts of a single-entity amphetamine product) as measured by the Swanson, Kotkin, Agler, M. Flynn and Pelham (SKAMP) deportment rating scale, a standardized, validated classroom assessment tool used for evaluating the behavioral symptoms of ADHD.3 Both treatments resulted in significantly improved behavior versus a

compared to placebo (P <.0001 for both medications) as measured by Permanent Product Measure of Performance (PERMP), an age-adjusted collection of math problems that measures a child's ability to pay attention and stay on task as demonstrated by an increase in the number of attempted and successfully completed problems.4

In the phase III, randomized, double-blind placebo-controlled study, all three doses of VYVANSE demonstrated significant improvements in ADHD Rating Scale (ADHD-RS-IV) scores compared with placebo (P <.0001) after four weeks of once-daily treatment. 5 ADHD-RS-IV is a standardized, validated test for assessing symptoms of ADHD in children and for assessing their response to treatment.6,7 This scale, which contains 18 items, is based on the ADHD diagnostic criteria as defined in the APA's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision®, a publication of the American Psychiatric Association. 8

Additionally, in a study presented in October at a major scientific meeting, VYVANSE yielded a 60 percent improvement in the primary rating scale scores for symptoms of ADHD in children aged 6 to 12 years who received six months of treatment in an open-label phase III study. Results also demonstrated that at 6 months, 95 percent of children taking VYVANSE produced a "much improved" or "very much improved" rating on the Clinical Global Impressions - Improvement score.9

About VYVANSE and ADDERALL XR

Tell your doctor about any heart conditions, including structural abnormalities, that you, your child, or a family member, may have. Inform your doctor immediately if you or your child develops symptoms that suggest heart problems, such as chest pain or fainting.

VYVANSE or Adderall XR should not be taken by patients who have advanced disease of the blood vessels (arteriosclerosis); symptomatic heart disease; moderate to severe high blood pressure; overactive thyroid gland (hyperthyroidism); known allergy or unusual reactions to drugs called sympathomimetic amines (for example, pseudoephedrine); seizures; glaucoma; a history of problems with alcohol or drugs; agitated states; taken a monoamine oxidase inhibitor (MAOI) within the last 14 days.

Tell your doctor before using VYVANSE or Adderall XR if you or your child are being treated for or have symptoms of depression (sadness, worthlessness, or hopelessness) or bipolar disorder; have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis; have had seizures or abnormal EEGs; have or have had high blood pressure; exhibit aggressive behavior or hostility. Tell your doctor immediately if any of these conditions or symptoms develop while using VYVANSE or Adderall XR.

Abuse of amphetamines may lead to dependence. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events. These events have also been reported rarely with amphetamine use.

VYVANSE and Adderall XR were generally well tolerated in clinical studies. The most common side effects in studies of VYVANSE included: children - decreased appetite, difficulty falling asleep, stomachache, and irritability. The most common side effects in studies of Adderall XR included: children - decreased appetite, difficulty falling asleep, stomachache, and emotional lability; adolescents - loss of appetite, difficulty falling asleep, stomachache, and weight loss; adults - dry mouth, loss of appetite, difficulty falling asleep, headache, and weight loss.

Aggression, new abnormal thoughts/behaviors, mania, growth suppression, worsening of motion or verbal tics and Tourette's syndrome have been associated with use of drugs of this type. Tell your doctor if you or your child have blurred vision while taking VYVANSE or Adderall XR.

The Collaboration Agreement

In January 2005, New River Pharmaceuticals signed a collaborative agreement with Shire to develop and commercialize VYVANSE. Details on the collaboration agreement are available in previous filings with the U.S. Securities and Exchange Commission.

Planned Acquisition Additional Information

The tender offer described in this press release has not yet commenced, and this press release is neither an offer to purchase nor a solicitation of an offer to sell New River common stock. Investors and security holders are urged to read both the tender offer statement and the solicitation/recommendation statement regarding the tender offer described in this report when they become available because they will contain important information. The tender offer statement will be filed by a subsidiary of Shire with the Securities and Exchange Commission (SEC), and the solicitation/recommendation statement will be filed by New River with the SEC. Investors and security holders may obtain a free copy of these statements (when available) and other documents filed by Shire or New River with the SEC at the website maintained by the SEC at www.sec.gov. The tender offer statement and related materials may be obtained for free by directing such requests to Shire at Hampshire International Business Park, Chineham, Basingstoke, Hampshire, England, RG24 8EP, attention: Investor Relations. The solicitation/recommendation statement and such other documents may be obtained by directing such requests to New River at 1881 Grove Avenue, Radford, Virginia 24141, attention: Director of Corporate Communications.

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About ADHD

Approximately 7.8 percent of all school-age children, or about 4.4 million U.S. children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the U.S. Centers for Disease Control and Prevention (CDC). 10 ADHD is one of the most common psychiatric disorders in children and adolescents. 11 ADHD is a neurobiological disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development.8 To be properly diagnosed with ADHD, a child needs to demonstrate at least six of nine symptoms of inattention; at least six of nine symptoms of hyperactivity/impulsivity; the onset of such symptoms before age 7 years; that some impairment from the symptoms is present in two or more settings (e.g., at school and home); that the symptoms continue for at least six months; and that there is clinically significant impairment in social, academic or occupational functioning.8

Although there is no "cure" for ADHD, there are accepted treatments that specifically target its symptoms. The most common standard treatments include educational approaches, psychological or behavioral modification, and medication.12

New River

New River Pharmaceuticals Inc. is a specialty pharmaceutical company developing novel pharmaceuticals that are generational improvements of widely prescribed drugs in large and growing markets. For further information on New River, please visit the Company's Web site at http://www.nrpharma.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

This press release contains certain forward-looking information that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995. Forward- looking statements are statements that are not historical facts. Words such as "expect(s)," "feel(s)," "believe(s)," "will," "may," "anticipate(s)" and similar expressions are intended to identify forward-looking statements. These statements include, but are not limited to, financial projections and estimates and their underlying assumptions; statements regarding plans, objectives and expectations with respect to future operations, products and services; and statements regarding future performance. Such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of New River Pharmaceuticals, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include: those discussed and identified in the New River Pharmaceuticals Inc. annual report on Form 10-K, filed with the SEC on March 15, 2006, as well as other public filings with the SEC; the timing, progress and likelihood of success of our product research and development programs; the timing and status of our preclinical and clinical development of potential drugs; the likelihood of success of our drug products in clinical trials and the regulatory approval process; our drug products' efficacy, abuse and tamper resistance, resistance to intravenous abuse, onset and duration of drug action, ability to provide protection from overdose, ability to improve patients' symptoms, incidence of adverse events, ability to reduce opioid tolerance, ability to reduce therapeutic variability, and ability to reduce the risks associated with certain therapies; the ability to develop, manufacture, launch and market our drug products; our projections for future revenues, profitability and ability to achieve certain threshold sales targets; our estimates regarding our capital requirements and our needs for additional financing; the likelihood of obtaining favorable scheduling and labeling of our drug products; the likelihood of regulatory approval under the Federal Food, Drug, and Cosmetic Act without having to conduct long and costly trials to generate all of the data which are often required in connection with a traditional new chemical entity; our ability to develop safer and improved versions of widely prescribed drugs using our Carrierwave (TM) technology; our success in developing our own sales and marketing capabilities for our lead product candidate; and our ability to obtain favorable patent claims. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. New River Pharmaceuticals does not undertake any obligation to republish revised forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. Readers are also urged to carefully review and consider the various disclosures in New River Pharmaceuticals' annual report on Form 10-K, filed with the SEC on March 15, 2006, as well as other public filings with the SEC.

Shire plc

Shire's strategic goal is to become the leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with a strategically aligned and relatively small-scale sales force will deliver strong results.

Shire's focused strategy is to develop and market products for specialty physicians. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

For further information on Shire, please visit the Company's website: www.shire.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's Attention Deficit and Hyperactivity Disorder (ADHD) franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD), SPD465 (extended release triple-bead mixed amphetamine salts) (ADHD); Shire's ability to secure new products for commercialization and/or development; Shire's planned acquisition of New River Pharmaceuticals announced February 20, 2007; and other risks and uncertainties detailed from time to time in Shire's and its predecessor registrant Shire Pharmaceuticals Group plc's filings with the Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2005.

1 data on file 2 New River Pharmaceuticals Inc. CONFIDENTIAL CLINICAL STUDY REPORT PROTOCOL NO.; LDX.301 "A Phase 3, Randomized, Multi-Center, Double-Blind, Parallel-Group, Placebo-Controlled Study of LDX in Children Aged 6-12 Years with Attention Deficit Hyperactivity Disorder (ADHD)," Final (4.0), 02 November 2005. 3 Wigal SB, Gupta S, Guinta S, Swanson JM. Reliability and Validity of the SKAMP Rating Scale in a Laboratory School Setting. Psychopharmacol Bull. 1998l 34 (1): 47-53. 4 "Improvements in Symptoms of Attention-Deficit/Hyperactivity Disorder in School-aged Children with Lisdexamfetamine (NRP104) and Mixed Amphetamine Salts, Extended-Release Versus Placebo," presented at the American Psychiatric Association, Toronto, Ontario, Canada, May 24, 2006. 5 "Efficacy and Safety of Lisdexamfetamine (NRP104) in Children Aged 6 to 12 Years With Attention-Deficit/Hyperactivity Disorder (ADHD)," presented at the American Psychiatric Association, Toronto, Ontario, Canada, May 24, 2006. 6 DuPaul G. Parent and Teacher Ratings of ADHD Symptoms: Psychometric Properties in a Community-Based Sample. Journal of Clinical Child Psychology. 1991; 20(3): 245-53. 7 Collett BR, Ohan JL, Meyers KM. Ten Year Review of Rating Scales. V: Scales Assessing Attention-Deficit/Hyperactivity Disorder. Journal of American Academic Child Adolescent Psychiatry. 2003; 42(9): 1015-37. 8 Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition, Text Revision. DSM-TR-IV®. Washington, DC: American Psychiatric Association; 2000: 85. 9 Childress AC, Krishnan S, McGough JJ, Findling RL. Interim Analysis of a Long-Term, Open-Label, Single-Arm Study of Lisdexamfetamine (LDX), an Amphetamine Prodrug, in children with ADHD. American Academy of Child and Adolescent Psychiatry Annual Meeting; 2006 Oct. 27; San Diego, CA: American Academy of Child and Adolescent Psychiatry; 2006. 10 Mental health in the United States: Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder, United States, 2003. MMWR, September 2, 2005;54(34):842-847. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5434a2.htm. Accessed September 27, 2005. 11 "Introduction," Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. NIH Consensus Statement 1998 Nov 16-18; 16(2): 1-37. Available at: http://consensus.nih.gov/cons/110/110_statement.htm#0_Abstract. Accessed on June 8, 2005. 12 Baumgartel A, et al. Practice guideline for the diagnosis and management of attention deficit hyperactivity disorder. Ambulatory Child Health. 1998;4:51.

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Press Release

Results of VYVANSE™ (lisdexamfetamine dimesylate) Pivotal Trial in Adult ADHD Presented at Major Scientific Meeting

All Doses of VYVANSE Studied Demonstrated Significant Efficacy Within One Week of Daily Treatment

BOSTON — October 25, 2007 — Shire plc (LSE: SHP, NASDAQ: SHPGY, TSX: SHQ), the global specialty biopharmaceutical company, today announced the results of a study which demonstrated that adults with Attention Deficit Hyperactivity Disorder (ADHD) experienced significant improvements in ADHD symptom control within one week of treatment with once-daily VYVANSE™ (lisdexamfetamine dimesylate), the first prodrug stimulant. Findings from this phase III pivotal trial were presented today at a national psychiatric meeting in Boston, Mass.

"Adults with ADHD may experience significant impairments in their ability to focus, and organize and complete tasks, which could affect their work, family life and personal relationships," said Lenard A. Adler, M.D., lead researcher in this study and director of the Adult ADHD Program at New York University School of Medicine and author of *Scattered Minds: Help and Hope for Adults with ADHD.* "The results of this study demonstrated that VYVANSE significantly improved the core symptoms of ADHD in adult study patients."

Results of Phase III Pivotal Trial
In this double-blind, placebo-controlled, four-week study with dose escalations in 414 adults aged 18 to 55 years, treatment with VYVANSE at all doses studied (30 mg, 50 mg, 70 mg) was significantly more effective than placebo and improvements were observed in the first week of the study.

All doses of VYVANSE showed significant improvements in the average change in ADHD Rating Scale (ADHD-RS-IV) scores, as measured from the study's start to end, the primary endpoint of this study. ADHD-RS-IV is a standardized, validated test for assessing symptoms of ADHD and for assessing their response to treatment. The scale, which contains 18 items, is based on the ADHD diagnostic criteria as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision®, a publication of the American Psychiatric Association.

VYVANSE provided a significant reduction in ADHD-RS-IV scores starting at week one that were observed throughout the full treatment period. At endpoint, VYVANSE provided a significant reduction in ADHD-RS-IV scores ranging from 16.2 to 18.6 points.

Investigators also measured the efficacy of VYVANSE with the Clinical Global Impressions-Improvement (CGI-I) scale, a standard assessment used to rate the severity of a patient's illness and improvement over time. The study found that the percentage of subjects taking VYVANSE rated improved on the CGI-I scale ranged from 57 to 61 percent across all doses and was significantly greater than placebo.

The study showed there were no statistically significant differences among the groups for total score of Pittsburgh Sleep Quality Index (PSQI) at endpoint with all groups showing a slight decrease in the PSQI total score at endpoint. The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a one-month time interval.

Adverse events reported in this study were generally mild to moderate and included dry mouth (26 percent), decreased appetite (27 percent) and insomnia (19 percent).

VYVANSE is a therapeutically inactive prodrug, in which *d*-amphetamine is covalently bonded to l-lysine, and after oral ingestion it is converted to pharmacologically active *d*-amphetamine. The pharmacokinetic profile of VYVANSE is inherent to its chemical prodrug nature and alterations in gastric pH and gastrointestinal motility do not affect its absorption.

A supplemental New Drug Application (sNDA) for VYVANSE for the treatment of ADHD in adults is currently under review by the U.S. Food and Drug Administration (FDA). VYVANSE is currently approved in the United States for the treatment of ADHD in children aged 6 to 12 years.

Additional information about VYVANSE and Full Prescribing Information are available at www.vyvanse.com.

About ADHD

Approximately 7.8 percent of all school-age children, or about 4.4 million U.S. children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the U.S. Centers for Disease Control and Prevention (CDC). ADHD is one of the most common psychiatric disorders in children and adolescents. The disorder is also estimated to affect 8.1 percent of adults, or approximately 9.2 million adults across the U.S. based on a retrospective survey of adults aged 18 to 44, projected to the full U.S. adult population. ADHD is a neurobiological disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. To be properly diagnosed with ADHD, a child needs to demonstrate at least six of nine symptoms of inattention; and/or at least six of nine symptoms of hyperactivity/impulsivity; the onset of which appears before age 7 years; that some impairment from the symptoms is present in two or more settings (e.g., at school and home); that the symptoms continue for at least six months; and that there is clinically significant impairment in social, academic or occupational functioning and the symptoms cannot be better explained by another psychiatric disorder.

Although there is no "cure" for ADHD, there are accepted treatments that specifically target its symptoms. The most common standard treatments include educational approaches, psychological or behavioral modification, and medication.

For further information please contact:

Porter Novelli for Shire

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Poster #B34
Efficacy and Safety of Lisdexamfetamine Dimesylate in Adults with ADHD
October 25, 2007; 11:00 a.m. EDT

About VYVANSE

Tell the doctor about any heart conditions, including structural abnormalities, that you, your child, or a family member, may have. Inform the doctor ***immediately*** if your child develops symptoms that suggest heart problems, such as chest pain or fainting.

VYVANSE should not be taken if your child has advanced disease of the blood vessels (arteriosclerosis); symptomatic heart disease; moderate to severe high blood pressure; overactive thyroid gland (hyperthyroidism); known allergy or unusual reactions to drugs called sympathomimetic amines (for example, pseudoephedrine); seizures; glaucoma; a history of problems with alcohol or drugs; agitated states; taken a monoamine oxidase inhibitor (MAOI) within the last 14 days.

Tell the doctor ***before*** taking VYVANSE if your child is being treated for or has symptoms of depression (sadness, worthlessness, or hopelessness) or bipolar disorder; has abnormal thought or visions, hears abnormal sounds, or has been diagnosed with psychosis; has had seizures or abnormal EEGs; has or has had high blood pressure; exhibits aggressive behavior or hostility. Tell the doctor ***immediately*** if your child develops any of these conditions or symptoms while taking VYVANSE.

Abuse of amphetamines may lead to dependence. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events. These events have also been reported rarely with amphetamine use.

VYVANSE was generally well tolerated in clinical studies. The most common side effects reported in studies of VYVANSE were decreased appetite, difficulty falling asleep, stomachache, and irritability.

Aggression, new abnormal thoughts/behaviors, mania, growth suppression, worsening of motion or verbal tics, and Tourette's syndrome have been associated with use of drugs of this type. Tell the doctor if your child has blurred vision while taking VYVANSE.

SHIRE PLC

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe. Shire believes that a carefully selected portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

For further information on Shire, please visit the Company's website: www.shire.com

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development (including the successful development of JUVISTA® (Human TGF 3)), manufacturing and commercialization (including the launch and establishment in the market of VYVANSE); the impact of competitive products, including, but not limited to the impact of those on Shire's Attention Deficit and Hyperactivity Disorder ("ADHD") franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval date of INTUNIV™ (guanfacine) extended release (ADHD) and GA-GCB (Gene-Activated Glucocerebrosidane); Shire's ability to secure new products for commercialization and/or development; Shire's ability to benefit from its acquisition of New River Pharmaceuticals Inc.; and other risks and uncertainties detailed from time to time in Shire plc's filings with the Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2006.

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/s/

Gary Buehler

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